SEVENTH FRAMEWORK PROGRAMME

mobi-kids

FP7-ENV-2008-226873
http://www.mbkds.net/

D2.1 Core Protocol

WP2 – Finalisation of the study instruments

Updated version

Lead beneficiary: GERTNER INSTITUTE
Date: 14/02/2012
Nature: Other
Dissemination level: PU

mobi-kids
Study on Communication Technology, Environment and Brain Tumours in Young People

MOBI-KIDS Protocol

10th version, updated to January 2012

Financial support for the study is provided by the European Union (grant agreement FP7-ENV-2008-226873) and local and national funding sources (see Annex A).

This document presents the standard procedures endorsed by the International Study Group for the conduct of the study. Further changes to the procedures will be discussed, as appropriate, at meetings of the Study Group or its subcommittees.

The document was written as part of a WP2 task by [redacted]. Formal proposals for changes should be sent in writing to email**:** [redacted]

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I. LIST OF PARTICIPATING CENTERS AND COLLABORATORS

Sixteen countries (and 18 centers) will participate in this project: 9 countries who receive funding from the EU (Austria, France, Germany, Greece, Israel, Italy, The Netherlands, Spain and United Kingdom) and 7 countries funded by other sources (Australia, Canada, New Zealand, Taiwan, Japan, India, and Korea).

Sixteen centers from these countries will participate in data collection, 1 center from Spain (FIMIM) will handle the project management and the center from the United Kingdom will contribute to exposure assessment. Additional countries may join subject on demonstrating feasibility and obtaining necessary funding. Following is the list of centers and collaborators and their roles in the study (Table 1):

	Country	Beneficiary short name	Collaborators	E-mail address	Role in the project	Institute	WP participation (person months)
DATA COLLECTION	***Austria***	MUVI	[redacted]	[redacted]	[redacted]	Institute of Environmental Health, and the Institute of Neurology of the Medizinische Universität Wien/Medical University of Vienna, Austria	WP1(24), WP2(3), WP3(3), WP5(5), WP6(2)
	Australia	MONASH	[redacted]	[redacted]	[redacted]	Centre for Occupational and Environmental Health, Monash University, Australia	WP1(49), WP2(3), WP3(3), WP4(5), WP5(5), WP6(2)
	Canada	UOTTAWA	[redacted]	[redacted]	[redacted]	McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, Faculty of Medicine, University of Ottawa, Ontario, Canada	WP1(38), WP2(3), WP3(3), WP5(5), WP6(2)
	France	ARECEA	[redacted]	[redacted]	[redacted]	Association pour la Recherche Epidémiologique dans les Cancers de l'Enfant et l'Adolescent.	WP1(53), WP2(3), WP3(3),, WP5(5), WP6(2)

	Country	Beneficiary short name	Collaborators	E-mail address	Role in the project	Institute	WP participation (person months)
DATA COLLECTION	***Germany***	LMU	[redacted]	[redacted]	[redacted]	Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine University Hospital of Munich (LMU)	WP6 Leader WP1(65), WP2(3), WP3(3), WP5(5), WP6(20), WP7(1)
	Greece	UOA-SARG	[redacted]	[redacted]	[redacted]	The Department of Hygiene, Epidemiology and Medical Statistics, National and Kapodistrian University of Athens, Greece.	WP1(18), WP2(3), WP3(3), WP5(5), WP6(2)
	Israel	GERTNER INSTITUTE	[redacted]	[redacted]	[redacted]	The Cancer & Radiation Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Tel Hashomer, Israel.	WP2 Leader WP1(27), WP2(20), WP3(6), WP5(5), WP6(2), WP7(1)
	Italy	UNITO	[redacted]	[redacted]	[redacted]	Cancer Epidemiology Unit (CEU) of the University of Turin/ Università degli Studi di Torino, Italy.	WP1(36), WP2(3), WP3(3), WP5(5), WP6(2)

	Country	Beneficiary short name	Collaborators	E-mail address	Role in the project	Institute	WP participation (person months)
DATA COLLECTION	***New Zealand***	AUKLAND UNI	[redacted]	[redacted]	[redacted]	The School of Population Health, The University of Auckland, New Zealand.	WP1(18), WP2(3), WP3(3), WP5(5), WP6(2)
	Spain	CREAL	[redacted]	[redacted]	[redacted]	Centre for Research in Environmental Epidemiology, Barcelona, Spain.	WP1 & WP5 Leader WP1(87), WP2(10), WP3(4), WP4(10),WP5(25), WP6(3), WP7(2)
		Andalucía	[redacted]	[redacted]	[redacted]	Universidad de Huelva-Andalucía	
		Madrid	[redacted]	[redacted]	[redacted]	Instituto de Salud Carlos III- Madrid	
		Valencia	[redacted]	[redacted]	[redacted]	Universitat de Valencia	
	Taiwan		[redacted]	[redacted]	[redacted]	National Taiwan University College of Public Health.	

Country		Beneficiary short name	Full name	E-mail address	Role in the project	Institute	WP participation (person months)
DATA COLLECTION	***The Netherlands***	UU				The Environmental Epidemiology Division of the Institute for Risk Assessment Sciences of Utrecht University,Netherlands, IRAS	WP3 Leader WP1(34), WP2(3), WP3(20), WP4(8), WP5(8), WP6(2), WP7(1)
	India	TMH				Tata Memorial Hospital	
	Japan	TWMU				Tokyo Women's Medical University	
		TMU				Tokyo Metropolitan University	
	Korea	DUCM				Dankook University College of Medicine	
PROJECT MANAGEMENT	***Spain***	FIMIM				Municipal Institute for Medical Research Barcelona, Spain	WP7 Leader WP6(10), WP7(28)
EXPOSURE ASSESSMENT	***France***	FT				The team "WAVE" of the Laboratory "SAFE", Telecom, France	WP2(1), WP4(7), WP6(1)
	United Kingdom	HPA				The Physical Dosimetry Dept. of Radiation Protection Division, Health Protection Agency. UK.	WP4 Leader WP2(2), WP4(15), WP5(2), WP6(1), WP7(1)

II. INTRODUCTION

A. Background

Mobile phone use has increased dramatically in many countries since its introduction in the early to-mid 1980s. This technology has brought with it some concerns about health and safety. In the late 1990s, several expert groups critically reviewed the evidence on health effects of low-level exposure to RF electromagnetic fields, and recommended research into the possible adverse health effects of mobile telephony. As a result, a multinational epidemiological study, INTERPHONE, was conducted in 13 countries (15 centers), to investigate whether mobile phone use increases the risk of cancer and more specifically, whether RF fields emitted by mobile phones are carcinogenic. The study focused on cases diagnosed between the ages of 30 and 59 years (the age range in which the prevalence of mobile phone use 5 to 10 years before the beginning of this study in 2000 was relatively frequent) and in most countries, it was restricted to the large urban areas where mobile phone use first started. The outcomes that were assessed in this study included gliomas, meningiomas, acoustic neurinomas and parotid gland tumors. Case ascertainment covered a period of 2 to 3 years between 2000 and 2004. Results of national analyses of the relation between mobile phone use and risk of specific tumor types in some of the participating countries have been published.

Pooling of data from Nordic countries and part of the UK yielded a significantly increased risk of **glioma** related to use of mobile phones for a period of 10 years or more on the side of the head where the tumor developed. Results for **acoustic neurinoma** are similar: the pooled analysis found a significantly increased risk of **acoustic neurinoma** related to durations of use of 10 years or more on the side of the head where the tumor developed. For **meningioma**, most national studies provided little evidence of an increased risk for short durations of use. For **parotid gland tumors**, the pooled analysis of data from Sweden and Denmark found a non-significantly increased risk of benign tumors for ipsilateral use for 10 years or more, with a decreased risk for contralateral use. In the much larger Israeli study, which included a substantially higher proportion of heavy users of mobile phones, the results suggest a possible relation between heavy mobile phone use and risk of parotid gland tumor.

More detailed analyses are also underway, focusing on more precise localization of tumors using 3-dimensional radiological images, and on the analysis of the effect of RF exposure at the location of the tumor, using a gradient of RF emitted by mobile phones. Adjustment for exposure measurement error based on data from the validation studies is also being conducted in order to assess the impact of these errors on risk. No information on risk from exposure in childhood was collected in the INTERPHONE study, as use in children at the time the study was started was still low.

The rapid worldwide increase in mobile phone use in adolescents and, more recently, children, has generated considerable interest in the possible health effects of exposure to radio frequency (RF) fields. Available information suggests that mobile phone use has been very prevalent among adolescents (15-18 years old), at least for the last five years. "Heavy" mobile phone use appeared to be rare, however, five years ago, among children below the age of 10. Concern originates from the fact that, if there is a risk, it is likely to be greater for use at these ages for the following reasons: the developing neurological system may be more sensitive to the effects of RF; the spatial distribution of RF energy absorption in the brain of children and adolescents may be different than that in adults; and because they start mobile phone use at an early age, and (at least for adolescents) tend to use phones

more than adults, children and adolescents are likely to have greater lifetime cumulative exposures to RF from mobile phones than those who started using the phones in adulthood.

Because of these concerns, a number of national and international bodies have recommended studies of exposure in childhood and adolescents as one of the high priority areas for RF research. These include the International EMF Project, the research agenda put forward by the EU-funded EMFNET coordination action, and the US National Research Council 2008 report. In addition, a number of national EMF research programs have defined this topic as a priority.

Because of the low prevalence of use of mobile telephones in children 5-10 years ago, and as the cancer risk, if any, is expected to be relatively small, inclusion of a large number of countries is essential in order to achieve sufficient power to detect an association between RF exposure and cancer risk if it exists.

The current study was initiated following the concern of the public and researchers regarding these exposures and as a response to a call from the European Union ENV.2008.1.2.1.1.for the topic: "Health impacts of exposure to radiofrequency fields in childhood and adolescence". This call aimed to estimate specifically the risk of potential adverse effects in the CNS (e.g., brain cancer) in childhood and adolescence. Financial support for the study is provided by the European Union (grant agreement FP7-ENV-2008-226873) and local and national funding sources.

III. OBJECTIVE

The **overall objective** of the current project is to assess the potential carcinogenic effects of childhood and adolescent exposure to radio frequency (RF) from mobile telephones on the central nervous system (CNS).

In order to achieve the overall objective of the project, the MOBI-KIDS **operational objectives** are the following:

- To conduct a multinational epidemiological case-control study of brain tumors diagnosed in young people in relation to EMF exposure from mobile telephones and other sources of RF in 9 countries under the EU grant, and in 6 non-European countries which are not funded by the EU grant.
- To develop and validate improved indices of RF and extremely low frequency (ELF) exposure, and assess related uncertainties, for all of the subjects in the study.
- To analyze the relation between risk of brain tumors and exposures to RF and ELF from mobile phones and other relevant and important sources of exposure in the general environment of young people.

The current project builds on the experience and difficulties encountered in the INTERPHONE study. In designing this study, major efforts are foreseen to improve on the design of INTERPHONE, including overcoming difficult epidemiological problems related to selection bias and recall errors and improving and optimizing the exposure assessment both for RF and ELF.

An important focus of the project will be the dissemination of knowledge about mobile phone exposure and health, as well as the results of the study to the general public, stakeholders in public health and the scientific community.

IV. STUDY METHODS

A. study design- This study is designed as a **prospective multinational case-control study of brain tumors.**

Rationale for study design-

A case-control approach was chosen over the cohort study as the most cost-efficient epidemiological design to address this issue at the international level. A cohort study design was also considered, but this approach was rejected because of logistic and ethical constraints in many of the interested countries. Prospective design was not chosen because of the extremely large cost which would be required to carry out a study with the same statistical power as a multi-centric case-control study (the study population would need to cover millions of persons, with individual exposure estimates) and because such a study would require years of follow up period.

B. study population-

Target population-

The target study population consists of all persons (males and females) aged 10-24 years who reside in the study regions. In some countries, the study region encompasses the entire country; while in others it has been restricted to defined areas. Table 2 describes the target population, study regions by center, and expected annual and total number of cases per country.

Table 2: Description of the Target study population, study regions, and expected annual and total number of cases by centre

Study center	Target study population	Study region	Size of source of population	Expected No. of cases	
				Per year	Per study
Austria				35	86
Australia	10-24 year olds in the 4 most populous states in Australia	4 States- Victoria, New South Wales, Queensland and Western Australia	N=2.4 million	71	178
Canada				94	234
France (source insee: estimation 2008)	Population 10-24	14 districts out of 6 regions: Lorraine, Alsace, Ile-de-France, Rhône-Alpes, Nord-Pas de Calais, Midi-Pyrénées	General population of these 14 districts (2008):17.7 M Population 10-24 (2008) :3.5 M	94	235

Study center	Target study population	Study region	Size of source of population	Expected No. of cases	
				Per year	Per study
Germany	Population aged 10-24 years	Nationwide	Total pop. (2009): 82 M	125	313
Greece	residents of Greece, aged 10-24 y	residents of Greece, aged 10-24 y	Population (Est. 2008): Total:~ 11.2 M 10-24 y: ~1.8 M	25	63
Israel	All citizens of Israel, aged 10-24 y	Nationwide	Total pop. (2009): 7.3 M. Age 10-24: 1.8 M	40	120
Italy	Residents in 4 northern and central Italian regions, aged 10-24 years	Piedmont, Lumbardy, Tuscany and Emilia Romagna	Total population (2009): 22.2 M. Age 10-24: 2.9 M	68	169
India	All citizens of mumbai, aged 10-24 y	Mumbai	Total population (2006): 13M. Age 10-24: 4.1M	40	100
Japan	Residents of Tokyo, aged 10-24 years	Tokyo Metropolitan area	Total: 12.6 M, 10-24: 1.7M (2010)	50	75
New Zealand				25	63
Spain	All residents of participating autonomous communities, aged 10-24 y	Autonomous communities of Andalucía, Catalonia, Madrid and Valencia	Total population (2009): 26.5 M. Age 10-24: 8 M	125	313
Taiwan					
Netherlands	All citizens of the Netherlands aged 10-24 y	Nationwide	Total population 16,5 million; age 10-24y: 3,0 million	84	210
Korea					
Total	-	-	-	786	1984

Sample size considerations-

About 750 cases of brain tumors are expected to be included in the study every year assuming a 20% refusal rate (with a total of about 1,450 cases in the European part of the study and 1,900 overall, including about 380 benign tumors). Table 3 shows the magnitude of the odds ratio (OR), that could be detected, with 80% power, based on an assumed alpha level of 0.05 and two controls per case and complete recruitment and participation of cases. Power calculations are shown in the table for different scenarios of exposure. Although the current prevalence of exposure (percentage of the population using mobile phones) in the study populations is higher than those shown in the table, the scenarios chosen are based on lower prevalence, reflecting use 7 or more years in the past, when, if there is a risk, we would expect the exposures of etiological relevance to have occurred. Thus, under the assumption that about 10% of the subjects have used mobile phones 7 years or more in the past, the study would have enough statistical power to detect increased risks of around 30%.

When the disease being studied is not common, such as CNS tumors in young ages, increasing the number of participating countries and enrolment of more than one control per case are the only ways to increase statistical power. While the importance of enrolling two controls per case and of incorporating centers outside Europe may not be obvious in the above calculations, they become essential for analyses of subgroups of tumors. Because RF energy absorption in the brain is very localized, the effect, if any, may be restricted to a small part of the total brain, of the order of one quarter or less of the brain tissue. It is therefore important that sufficient power is available to study such effects which would then be apparent only in a subgroup of cases, of the order of 300 or 400. A subgroup of 300 cases would correspond to 20% of the total number of cases in the European study and 15% in a study including non-European centers. The gain of enrolling 2 controls per case in a study of a subgroup of 300 cases would result in having the power to detect an OR of 1.8 compared to an OR of 2.0 if only 1 control per case was enrolled.
It should be noted that any power calculation is only indicative, since it is very difficult to evaluate, a priori, the effects of missing values, misclassification, lower than 100% recruitment and confounding. It is for this reason that a very high power is proposed since the study should be able to detect even a very low increased risk. No power calculations are presented for interactions including gene-environment interactions since these do not form part of the proposed study. Such interactions will be considered only if a main effect of the environmental exposure (mobiles) can be documented.

Table 3: Size of the Odds Ratio that can be identified under different scenarios with 80% power

Prevalence of exposure (5-10 years in the past)	**Number of cases** (2 controls per case)	**OR that could be identified**
20%	1, 455 European component 1, 929 Entire study	1.25 1.21
10%	1, 455 European component 1, 929 Entire study	1.33 1.28
5%	1, 455 European component	1.47

	1, 929 Entire study	1.40

Case selection and definition-

Rationale for the choice of cases-
It was decided to focus the study on benign and malignant brain tumors. These tumors were chosen as they occur in some of the tissues thought to have the highest exposure to RF and ELF from mobile phones.
Different types of brain tumors show strong age dependence. In the age range of interest (10-24 years), most tumors appear to be gliomas. Preliminary data indicate that benign brain tumors represent about 20% of all brain tumors. Because these tumors are seen in the same departments and share some risk factors with malignant tumors, benign brain tumors will also be included in the study.

Case definition (inclusion criteria)-
The cases will be all patients aged 10-24 years (from the 10th birthday and younger than 25 years old) from the target population (see Table 2) with a confirmed diagnosis of a first primary brain tumor, who are diagnosed during the study period (about two and a half years; the earliest diagnosis will be between July 2010 to July 2011 depending on the centre, and the latest diagnosis will be in August 2013), who resides in the study region and who have given informed consent (either themselves and/or their parent/guardian as applicable).
Cases should be histologically confirmed, either from surgery or biopsy material. Only when biopsy or surgery was not performed, cases could be included on the basis of unequivocal imaging results.
Coding of the diagnosis will be according to the International Classification of Diseases (ICD) Version 10 or O (revision 3). The list of eligible topologies and morphologies is provided in Annex B.

Date of diagnosis (reference date) will be the date of first imaging showing suspicion of a SOL (space occupying lesion) that eventually was diagnosed as a brain tumor.
Citizens who have been operated in foreign countries will be included in the study if pathology reports are available.

Residency in the study region may be a country specific criterion.

Residents that are not citizens of the country could be included in the study. In many countries this sub population is a substantial proportion of the total population and their children speak the local language making it possible to interview them.

Exclusion criteria - Insufficient knowledge of the main languages of the study (see Table 2). The decision to exclude cases due to language barrier will depend on the interviewer judgment. Patients with known genetic syndromes related to BT (e.g. Neurofibromatosis, Turcot syndrome, Tuberous sclerosis, etc.) will be excluded as soon as data regarding the genetic syndrome will be available (before the interview or at the time of data analysis).

Non-residence or cases that do not live in the study area – only those who live in the study region for more than 6 m will be included (in India more than 1 year).

* Cases that were recruited according to the previous definition of reference date (date of operation) and were interviewed before May 2011 will be included only if their 1st imaging is up to 3m before data collection started.
* Cases that will be diagnosed according to imaging reports during the study period will be included in the study even if the date of surgery will be later than last date of data collection.

The definition of "non operable case" could change during the study period.

* If the data collection will not be ended by the planned date, a request will have to be made to the EU for more time**.**

Control selection and definition-

Rationale for choice of control –
Recent years have shown a major decline in participation rates amongst controls selected from the general population. The experience of INTERPHONE has confirmed this, with an overall participation among controls of 54%. Participation has been shown to be selective with respect to phone use thus complicating the interpretation of the study results. Considering the age range that is proposed in the current study, the problem of selective participation is likely to be relevant in the study. The source population is younger than in many other cancer studies and at an age when other preoccupations may be major impediments to participation.

In order to minimize non-participation, controls will be selected among subjects who were operated due to suspected appendicitis, a disease that is common in all age ranges included in the study and not related to mobile telephone use or SES (Socio-Economic Status). This will ensure that the controls are representative of the general population from which the cases arise.

Control definition
Two hospital controls will be selected per case. Post operative Patients who were operated (either open surgery or laparoscopy) due to suspected appendicitis (ICD10 K35.0-35.9: including acute appendicitis with generalized peritonitis, acute appendicitis with peritoneal abscess and acute appendicitis, unspecified) will be included.

Control selection will run in parallel to case ascertainment. The date of surgery of the controls should be within ± **3** months from the date of surgery of the case (or date of interview if surgery was not performed).

Care will be taken to select controls from the same population base as cases (see Table 4). The latter issue will be taken care of by the proper selection of the medical institutions that will be chosen for the study.

Controls will be **individually** matched to cases on age (**±1y for cases less than 17 years and ±2y for cases 17 years and older; the minimum age for controls will be 10 and the maximum 24y**), sex and residency in the same geographical areas as the case.

In the event that no matched control is identified, the following steps should be taken:

1) Expand the geographical area, keeping the age and date (±3 months from the case's surgery date) criteria. If there are still no eligible controls, then:
2) Widen the date of surgery for the control by one month (±4 months from the case's surgery date). If there are still no eligible controls, then:
3) Widen the age by 6 month increments (±1.5 years for cases less than 17 years old and ±2.5 years for cases 17 years and older).

Exclusion criteria- History of a brain tumor, insufficient knowledge of the main languages of the study regions (the decision to exclude control due to language barrier will depend on the interviewer judgment), mental disability or non residents depending on the country (see Table 2). Controls with known genetic syndromes related to BT (e.g Neurofibromatosis,

Turcot syndrome, Tuberous sclerosis, etc.) will be excluded as soon as data regarding the genetic syndrome will be available (before or after the interview).

Table 4: Source of control ascertainment by center

Study center	Source of control ascertainment
Austria	
Australia	Appendicitis cases from major hospitals in 3 capital cities i.e Melbourne, Sydney, and Perth.
Canada	
France	General surgery/Visceral surgery/ Emergency Units
Germany	General and paediatric hospitals of the same regions where cases are recruited.
Greece	Surgery departments of General and Children's Hospitals of the same region where cases are recruited.
Israel	Adults and children general surgery departments that cover all Israel region, including hospitals with neurosurgery departments and a sample of additional medical centers in areas from which cases are recruited (list of medical centers will be available later).
Italy	In each of the 4 Italian regions: the main regional hospital (in the region capital city) + 2 to 4 general hospitals located in different provinces capturing population from rural areas and towns
India	Surgery departments of same regions from where cases are recruited
Japan	Adults and children general surgery departments and emergency units , in 2 provinces in Tokyo
New Zealand	
Spain	In each of the 4 Spanish regions: the main regional hospital (in the region capital city) + 2 to 4 general hospitals located in different provinces capturing population from rural areas and towns.
Taiwan	
Netherlands	A sample of regional hospitals with a pediatric department covering all Dutch regions.
Korea	3 hospitals for case selection and 2 hospitals for controls in Seoul and Gyunggi regions.

C. Case identification & ascertainment

Rationale for rapid case ascertainment –

Case ascertainment should be rapid (preferably within one month of diagnosis) so that interviews can be scheduled as soon as possible after diagnosis, in order to minimize the number of cases whose participation may be restricted by death or deteriorating health.

Primary source for case ascertainment-

The primary source for ascertainment of brain tumors will be the relevant departments (neurosurgery, radiology, oncology etc) of the participating health institutions. Treatment for brain tumors is mainly done in a limited number of specialist clinics in each country. Care should be taken to identify and recruit all cases resident in the study region even if operated or treated outside of the study region. Therefore, more than one source of identification is recommended.

It should be emphasized that selected number of additional adult and children surgery departments will be added to the study. The choice of these departments will depend on the particular health structure in each country (e.g. to cover the same geographical area, HMOs clinics, private/public clinics etc.)

Secondary source for case ascertainment-

Where population-based or hospital-based cancer registries exist, they should be used as a secondary source to ensure the completeness of the case ascertainment for malignant tumors (and benign tumors where they are registered).

The country specific source of case ascertainment is summarized in table 5.

Table 5: Source of case ascertainment by center

Study center	Source of case ascertainment
Austria	
Australia	Neurosurgery, Oncology, Neuroradiology and neuropathology departments in participating hospitals
Canada	
France	Neurosurgery / Neuroradiology/ Neurology Units
Germany	Mainly neurosurgery but also oncology departments in collaborating hospitals (paediatric and adult departments)
Greece	Children and young adults treated at all the neurosurgery, oncology, radiotherapy and radiology departments in Athens, Thessaloniki and the 5 major University Hospitals all over Greece, that have agreed to participate
Israel	Adults and children neurosurgery/oncology/radiology units in 5 medical centers (covering all Israel except for one center)
Italy	All the relevant departments within the study regions Regional and extra-regional hospital discharge records
India	Neurosurgery, Oncology, Neuroradiology and radiotherapy departments in participating hospitals
Japan	Neurosurgery and oncology departments in collaborating hospitals for children and adults
New Zealand	
Spain	Primary: all the relevant departments (Neurosurgery, Oncology, Radiation therapy, Pathology, hospital discharge) of participating hospitals. Secondary: Cancer registry in Valencia, Cataluña and parts of Andalucía. Hospital-based cancer registry in Madrid.
Taiwan	
Netherlands	Participating neurology/neuro-oncology departments for children and adults.
Korea	Researchers in neurosurgery department of 3 hospitals among big 5 hospitals in Seoul.

General procedures for case ascertainment-

As the health system in most countries becomes increasingly overworked, the health professionals do not always have time to bear in mind the existence of a study such as this. Experience has shown that throughout the period of case accrual it is essential to maintain a close relationship with these departments to ensure that cases are not missed and that the required authorizations are obtained from treating physicians when necessary.

Therefore, close monitoring of case ascertainment is essential in order to ensure rapid access to patients for interview as soon as possible after diagnosis.

An active ascertainment method such as weekly contact with the relevant departments should be implemented.

Validation of eligibility for participating in the study-

Before recruitment, the eligibility for participation should be evaluated by:

a. Brain tumor diagnosis- the exact diagnosis should appear in the list of eligible diagnoses (Annex B).

b. The diagnosis should be specified in a pathology record (or radiology report when no surgery/biopsy was performed).

c. The date of diagnosis should be within the study period.

d. Compatibility regarding age, study region and other inclusion and exclusion criteria should be checked.

* Individuals who will be found as non eligible will be excluded even if they have been recruited and interviewed.

D. Control Identification & Ascertainment:

Rationale for rapid control ascertainment –

Because of the rapid evolution of mobile phone use it is important that cases and their matched controls are interviewed within a narrowed time window (preferably within ±3 months from case surgery/interview).

Control ascertainment should be rapid so that interviews can be scheduled as soon as possible in order to be able to interview the controls with minimal delay following the identification of the case. Attempt to recruit controls can be made up to 8 times at different hours of the day before moving on to another control. The recruitment process should be detailed in a report.

Source for control ascertainment-

The primary source for the controls will be the relevant departments in which patients are operated (surgery, pediatrics etc) of the selected health institutions chosen to be representative of the target population. The health institutions will be selected by each centre. Country specific ascertainment procedures for controls are specified in Table 6.

E. Recruitment of the cases and controls:

All cases and controls will be contacted, informed about the study, and asked to participate in the study. The methods of contacting the eligible participants will differ according to the study centre.

Country-specific case and controls ascertainment procedures -

Each country will have to establish active procedures for the ascertainment of cases from participating health institutions. Table 6 shows specific recruitment protocols for cases and controls in each country. The study periods for each centre are summarized in Table 7.

Table 6: Methods of cases and controls recruitment by center

Study center	Method of case recruitment	Method of control recruitment
Austria		
Australia	Active ascertainment through regular contact with the relevant departments	Active ascertainment through periodic contact with selected representative hospitals
Canada		
France	Mobi-kids posters and flyers in Units. Mobi-kids medical referent in each participating units'. Direct contact while hospitalization or solicitation by mail/phone call through units secretariat if no hospitalization or too short, too tired.	Mobi-kids posters and flyers in Units. Mobi-kids medical referent in each participating units'. Direct contact while hospitalization or solicitation by mail/phone call through units secretariat if no hospitalization or too short, too tired.
Germany	New cases will be identified by collaborating physicians in the participating departments. These will be regularly contacted by e-mail and/or phone to ask whether new cases have come in. After permission for participation, the cases (& parents) will be contacted by the interviewer to obtain informed consent and to schedule an interview.	Once a new eligible case has been contacted, participating general surgery departments for pediatric or adult patients will be contacted to ask for matched controls. Hospital staff will inform eligible controls. After permission for participation, the controls and parents will be contacted by the interviewer to obtain informed consent and to schedule an interview.
Greece	Weekly contact with the designated Mobi-kids contact-person in each participating dept (resident/nurse/secretary etc). Direct contact during hospitalization or at other scheduled hospital visit. Following identification of a potential case, and confirmation of eligibility criteria: In Athens: the health visitor will proceed to the interview. In regional hospitals: the designated contact person (medical resident) will	Weekly contact with the designated Mobi-kids contact-person in each participating dept (resident/nurse/secretary etc). Direct contact during hospitalization or at other scheduled hospital visit. Following identification of a potential case, and confirmation of eligibility criteria: In Athens: the health visitor will proceed to the interview. In regional hospitals: the designated

Study center	Method of case recruitment	Method of control recruitment
	conduct the interview.	contact person (medical resident) will conduct the interview.
Israel	Cases identified in neurosurgery/oncology departments: the field interviewers (nurses and medical students) in the five medical centers routinely examine the neurosurgery departments' admissions (1-2 visits per week). Following identification of a potential case, the staff verifies the eligibility criteria, notify the case to the study centre and then proceed for an interview. Cases identified in archives and pathology departments: The central study nurse is responsible for additional cases of brain tumors which were missed by the interviewers. She identifies potential cases from the above-mentioned sources, contacts the case by telephone and verifies the eligibility criteria including date and mode of diagnosis. After obtaining consent to participate in the study, she prepares the case for a subsequent contact with the interviewer to schedule an interview.	Controls identified in general surgery departments: the field interviewers (nurses and medical students) in the 5 medical centers where cases are recruited from and additional medical centers (4) placed in regions which cases arrive from , routinely examine the surgery departments' admissions (1-2 visits per week). Following identification of a potential control, the staff verifies the eligibility criteria, notify the control to the study centre and then proceed for an interview.
Italy	Active ascertainment through weekly contact with the relevant departments	Active ascertainment through periodic (monthly) contact with the selected representative hospitals
India	Active recruitment through daily contact with the relevant department of all participating hospitals	Active ascertainment through periodic (weekly) contact with the selected representative hospitals
Japan	Active ascertainment through regular contact with the relevant departments	Active ascertainment through regular contact with the relevant departments
New Zealand		
Spain	Weekly contact with relevant departments of the participating hospitals asking about whether new cases have come in. In most hospitals, the study will be presented by the hospital staff to the case or his/her guardian and informed consent will be sought before the interviewer comes to the hospital. In a few hospitals, it is possible that the interviewer will be the one to present the study and seek informed consent.	Active ascertainment through periodic (monthly) contact with the selected representative hospitals
Taiwan		
Netherlands	For pediatric cases (10-17y): new cases will be identified and recruited by	Once a new eligible case has been contacted, participating general

Study center	Method of case recruitment	Method of control recruitment
	pediatric oncologists and entered into a registration database of pediatric brain tumor patients. After permission for participation, the cases & parents will be contacted by the interviewer to obtain informed consent and to schedule an interview. For adult cases (18-24y): new cases will be identified and recruited by neuro-oncologists. Participating neurology/neuro-oncology departments will be regularly contacted by e-mail and/or phone to ask whether new cases have come in. After permission for participation, the cases (& parents) will be contacted by the interviewer to obtain informed consent and to schedule an interview.	surgery departments for pediatric or adult patients will be contacted to ask for matched controls. Hospital staff will inform and recruit eligible controls. After permission for participation, the controls and parents will be contacted by the interviewer to obtain informed consent and to schedule an interview.
Korea		

Table 7: Recruitment period by center

CENTER	CASES						CONTROLS			
	1ST date of brain tumor diagnosis	Last date of brain tumor diagnosis	Start date for case recruitment	End date for case recruitment	Start date for case interview	End date for case interview	Start date for control recruitment	End date for control recruitment	Start date for control interview	End date for control interview
Austria										
Australia	01/05/11	30/04/13	01/05/11	30/05/13	01/05/11	30/06/13	01/05/11	30/08/13	01/05/11	30/09/13
Canada										
France forecast schedule can change	September 2010	Mars 2013	September 2010	Mars 2013	September 2010	Mars 2013	October 2010	June 2013	October 2010	June 2013
Germany	01/10/10	31/08/13	01/10/10	31/08/13	01/10/10	30/09/13	01/10/10	30/11/13	01/10/10	30/11/13
Greece										
Israel	01/09/10	28/02/13	01/09/10	28/02/13	01/09/10	29/03/13	01/09/10	31/05/13	01/09/10	30/09/13
Italy	01/09/10	28/02/13	01/09/10	28/02/13	01/09/10	29/03/13	01/09/10	31/05/13	01/09/10	30/09/13
India	01/03/2011	31/08/2013	01/06/2011	31/08/2013	01/06/2011	31/08/2013	01/06/2011	31/08/2013	01/06/2011	31/08/2013
Japan	01/06/11	31/12/12	01/06/11	31/12/12	01/06/11	31/01/13	01/06/11	31/12/12	01/06/11	31/01/13
New Zealand										
Spain										

Taiwan										
Netherlands	01/11/10	31/08/13	01/11/10	31/08/13	01/11/10	30/09/13	01/11/10	30/11/13	01/11/10	30/11/13
Korea										

Ethical considerations-

Ethics approval for conducting the study will be obtained from each centre in accordance with the local institutional ethics committees. Procedure regarding the local approval to conduct the study and for consent procedure must be in accordance with the study protocol. Any requested deviation from the protocol should be submitted for discussion to the epidemiology subcommittee.
Since this study involves adults and children, and various countries, consent requirements will vary between centers, depending on local ethics committees. Informed consent will be given by the index or guardian or both depending on legal age for transition to adulthood in each country.
Individual participating centers will inform the study coordinators (CREAL) when ethical approval has been obtained and forward a copy of the ethic approval and consent form used (in the original language).

Informed consent-

After a thorough explanation of the study aims and methods all subjects who agree to participate will approve their participation by signing an informed consent form. Each country will develop a *specific protocol for this procedure. The country specific protocols of the informed consent procedures are summarized in Annex C.*

Response rates among cases and controls-

Direct participation of cases and controls must be maximized because proxy information, especially concerning habits of use of mobile phones and other devices, could be less reliable. **A target of at least 80% participation rate in cases and in controls will be considered good.**
Lower response rates among controls are often a problem in case control studies. There are ways to improve these response rates, but they may not always be feasible in all countries.

It is important to try to set up interview procedures that do not impose a significant burden on the participants. In the age group included in the study, parental approval may be a serious issue leading to high refusal rates. Interviewers should be flexible and available to accommodate the participants' schedules and interview location. In addition, interviewers should allow conducting the interview with or without the presence of the guardian according to the parent's preferences and the specific local regulations.

Introductory material sent to the study subjects should be very simple and clear and as far as possible attempt to distinguish the study from the plethora of marketing information with which people are increasingly bombarded. It is important that someone in the study office be readily available to provide information. A website containing information on the study may be of interest to many potential participants.

F. Documentation of participation and refusal-

A follow up data base will be provided in which every potential study subject should be entered including demographic information, outcome of all contacts, final participation status and in case of refusal, reasons for non-participation (see Annex D). Non participants will be asked to complete a short refusal questionnaire (see Annex E).

V. Data collection for the main study

Data collection will be performed by using a personal questionnaire including information on demographic variables and data on potential risk factors, abstraction of clinical data and localization of tumors using images preferably (imaging records can be used where images are not available).

A. Personal Interviews-

Interview protocol-

- Personal data should be collected in a face to face interview conducted by a trained interviewer. Only in countries/cases where this method is not feasible, phone interviews will be conducted (with the option of sending the questionnaire prior to interview by mail or to use the internet).

In the parental questionnaire it is preferable to interview the mother, if this is not possible, the father should be interviewed. Only if either one of the parents are not available, the index should respond to the parental questionnaire. Yet, data for the parental questionnaire could be retrieved by a phone interview, email or by mail.

- In case of an adopted index where the relevant details for one or both of the parents are not available, unknown should be marked in the relevant questions and a note should be made in the comments at the end of the questionnaire.

Timing of interview

Ideally, the interview should be conducted as soon as possible after diagnosis – preferably within 4 weeks after diagnosis for cases and within ±3 months from the case surgery or interview (if the case was not operated) of case for the matched control. This may not always be feasible, given constraints placed by ethics committees on access to cases and authorization by treating physicians, and the logistics of finding suitable controls.

Controls might be interviewed before cases but this must be within the time window of 3 months.

Once an interview has been planned, the participant's details, study identification number, name, current address, date of birth, sex, and the interviewer's name are entered into the Appendix by the interviewer or a study coordinator, depending on the country.

In countries where appointments are made in advance, the subject will be asked, if appropriate, to bring his/her billing records and information on his/her previous mobile telephones to the interview.

When the study subject cannot complete the interview in one sitting (too tired or ill, etc), the interviewer will make another appointment to complete the questionnaire at a later time and this will be noted in the appropriate section of the questionnaire.

To lower the travel costs, each country be divided by region and in each region interviews will be performed by different interviewers.

In the event that an interview is performed with the help of a translator, documentation will be made in the questionnaire (question H.5). Table 8 summarizes the language of interview in each country.

Table 8: Languages of interview in each country

Study center	Main languages	Other languages using translator
Austria	German	
Australia	English	
Canada	English	French?
France	French	North African, African and Eastern Europe languages
Germany	German	
Greece	Greek	-
Israel	Hebrew	Russian, Arabic
Italy	Italian	none
India	English, Hindi, Marathi	none
Japan	Japanese	none
New Zealand	English	
Spain	Spanish	Catalan
Taiwan		
Netherlands	Dutch	Turkish, Arabic
Korea	Korean	

The interviewers-

While there are no restrictions regarding the profession of the interviewers, they must have been trained in the administration of the questionnaires at the national level. The national interviewers will be trained centrally during an interviewer training workshop (28.4.2010). Periodic local workshops will be conducted to ensure consistent reliability in the data collection. A central retraining workshop will also be organized 6 months after the start of data collection in the majority of countries. As the tumors of interest are rare, the number of interviewers should be kept to a minimum.

- Periodic interviewer's workshops are necessary every 3 months. The Gertner Institute will send agenda and slides for the workshops in order to maintain uniformity between all study centers.
- Before data collection starts, Skype conference calls will be performed for every few centers from the same geographical area.

It will be important to ensure that similar proportion of cases and controls will be interviewed by each interviewer.

Specific details on the interview procedures in each centre are described in Table 9.

Table 9: Interviewing procedure by center

center	Type of interview (personal/ phone/ internet)	Profession of interviewers	Location of interview	Computerized questionnaire (Yes/no)	Interviewee by age		
					Index	Guardian	Both
Austria							
Australia	Face to face interview	Research assistants	Home or hospital	Yes	< 18 years with parent or guardian, > 18 years alone or with parent or guardian if necessary	For parental questionnaire and when an individual cannot answer	Whenever possible
Canada							
France	Face to face as much as possible	Technical research assistants	Home or monitoring visit at the hospital	yes	18-24 alone or with parents 10-18 with parents	10-24 if index too ill, too tired or dead	10-18
Germany	Preferably face to face; for parents also possible by phone or mail.	Research assistants. students	Hospital/home	Yes	10-17 yrs: in the presence of a parent; 18-24 yrs: alone or with parent	If index cannot answer	Whenever possible
Greece	Face to face	Health visitor	Hospital	Preferably yes	<18 yrs with parent >18 yrs can be alone	when index cannot answer	When ever possible
Israel	Face to face	Nurses/ students	Hospital/ Home	Not sure yet	10-16index with patent/guardian;	Only if index cannot answer	Whenever possible
Italy	Preferably personal; Phone when personal interview is impossible	Professional/experienced interviewer (not doctors, nurses and students)	Preferably hospital during index's stay Home otherwise	yes	10-18 y: in the presence of a parent; 18-24 y: alone or with parent (so to interview personally also the	Only if index cannot answer	Whenever possible

					parent)		
India	Face to face interview	Scientific Assistant	Hospital	Preferably yes	18-24 alone or with parents 10-18 with parents	10-24 if index too ill, to tired or dead	10-18
Japan	Face to face interview	Research assistants	Hospital	Yes	< 18 years with parent or guardian, > 18 years alone or with parent or guardian if necessary	For parental question naire and when an individual cannot answer	Whenev er possible
New Zealand							
Spain	In person	Nurse/ others?	Hospital where possible	Yes	<18 years with parent; 18 years or more can be alone	When index cannot answer	When ever possible
Taiwan							
Netherlands	Preferably face to face; for parent also possible by phone or mail.	Experienced interviewer	Hospital/Ho me	Yes	10-17 y: in the presence of a parent; 18-24 y: alone or with parent	Necessary when index is 10-17y; preferably also present when index is older, in case index cannot answer.	
Korea							

The interview-

The questionnaire includes sections that refer to the index and to the parents. As the study population includes individuals of different ages (children, adolescents and adults), there are differences between them with respect to recall of exposures and their legal eligibility to participate independently (without their guardian) in an interview. This may vary among the participating countries (see Table 9).

- The parental questionnaire includes exposures mainly of the mother and to a lesser extent of the father. Therefore, it is preferable that the interviewee for this part will be the mother (alone or with the father). If the mother is not present during the index interview, the parental questionnaire can be administered by phone or mail Questionnaire. It is preferable to interview the mother, if this is not possible, the father should be interviewed. Only if either one of the parents are not available, the index should respond to the parental questionnaire.

Use of proxy: In the situation where subjects are too ill, confused, or mentally disabled with little possibility of recovery, or have died, a proxy respondent may be used. The proxy should be a parent or a guardian. In the exceptional case where this is not possible, a judgment will be made in collaboration with CREAL depending on the individual case. There will be no proxy interviews for controls.

A manual detailing guidelines for this interview is added in Annex F.

Personal questionnaire-

The questionnaire (Annex G) was developed, based on the INTERPHONE questionnaire, modified in light of the experience obtained in that study and simplified for administration to younger subjects. It was constructed by members of the Gertner Institute (as part of leading WP2) with the contribution of the epidemiology subcommittee, the exposure assessment subcommittee (WP4) and all study members. The questionnaire was pilot tested on volunteers in a number of different countries before its finalization.

The study questionnaires concern information on the following variables:

Main questionnaire: General information; home addresses; residences in a farm; residential exposure to animals; laterality/handedness; mobile phone use including: mobile phone identification & calendar, mobile phone operators, mobile phone use (start, recent, changes), mobile phone usage other than voice call; other wireless communication device usage; cordless phone use (start, recent, changes); WiFi use at home, school & work; exposure to other (non communication) sources of ELF & RF including: electrical appliances, occupational history, medical radiation including: X-Ray, CT scan, MRI scan, angiograph, dental x-ray: bite-wing x ray, full mouth x ray, panorex X ray, dental CT, therapeutic radiation; and medical history including other cancers and allergies.

Maternal questionnaire: education; details regarding pregnancy with the index including: medical history, infectious diseases, medication use, exposure to UV & X-Ray, alcohol intake, mobile phone use, electrical appliance usage, maternal smoking history, fertility, and child's delivery; maternal occupational history; index's school history; and family history of cancer.

Father's questionnaire: education, paternal occupational history.

The questionnaire was developed centrally in order to ensure compatibility between countries. It has been translated in the different languages of the study at the national level and back translated into English to verify the adequacy of the translation.

This core questionnaire includes 3 parts:

a. Details for communication and data on the interviewee (for the main questionnaire and for the parental questionnaire, see Annex H)
b. Main questionnaire (index data)
c. Parental questionnaire (maternal & paternal data)

Additional sections on potential risk factors may be added in some countries. These will be included in specific models and added at the end of the main questionnaire. Site specific questions are listed in Annex I.
A code book will be part of the database.

Supplementary Material for Questionnaire-

Several supplements will be developed to improve the understanding of the questionnaire and recall of the interviewees. These include: a glossary for the terms that appear in the questionnaire (that include definitions of all medical, technical and other terms that might not be understandable to all people) (Annex J) and data base of mobile phones. Pictures of mobile phones which were and are used in each country will be available in a computer file.

Non-respondents –

Individuals who refused to participate in a full interview will be asked to complete a short refusal questionnaire (NRQ) to evaluate whether they differ from those who agreed to participate in the full interview with respect to mobile phone use and some other variables (Annex E).

B. Clinical data

Information on clinical data including localization of tumor will be collected into specialized data bases. It is important that the location of all brain tumors is recorded as accurately as possible. Study centers will require the services of a neuroradiologist to ensure that high-quality tumor location data are collected from MRIs or CTs or imaging records if the original images are not available.

Medical reports–

Copies of the radiology report, surgery reports, pathology and discharge reports should be collected and retained.
Data from these reports will be abstracted into clinical questionnaire (Annex K).

Images-

Each study centre will attempt to locate diagnostic MRI or CT images for all brain tumor cases. These will be reviewed by a neuroradiologist who will record the location. A special protocol for tumor localization is included in Annex L.

Histology slides-

For a sample of cases (at least 10%), histological (or electronical) slides will be collected and sent to the coordinating center for central verification of the diagnosis (Annex M).

VI. Validation of data

Validation of diagnoses -

The verification of diagnosis of brain tumors shall be conducted by a small international group of neuropathologists who will come together periodically during the study. They will verify the original diagnoses on a 10% sample of cases based on the collected information (slides, notes, etc.) (see Annex M).

Validation of mobile phone use-

Self-reports of past mobile phone use may be prone to error and there will be little point in attempting major efforts at exposure estimation if the information on phone use is inadequate. In the current study, every effort will be made to collect (with the subject's consent) historical information from network operators about the subject's past use of mobile phones, including number and duration of calls, voice vs. data use, and, where possible, use of prepaid cards. The self-reported information will be compared to the historical use information (corrected for % use of the phone by index) and comparability will be assessed.

The exact protocol for validation of mobile phone use is detailed on Annex N; the validation conducted in each center is described in Table 10.

It is important to initiate contacts with the network operators in each country as soon as possible for the purpose of validation of mobile phone use. It usually takes a long time and therefore it is preferable to create this contact before the study starts.

Validation of other data

Logic checks will be built in the digital questionnaire to minimize erroneous answers. Centers will check the questionnaire within two weeks after collection to verify the completeness and correctness of the data. In case of possible problems the centers will re-contact the interviewee to check the responses. The study centers will submit their completed questionnaires (periodically) to the coordinating centers, where, in conjunction with WP3, the response distributions of all items will be explored to see if there are any indications of data differences between centers (Annex P).

Table 10: Mobile phone use validation and tumor localization procedure by center

Study center	Method of Mobile phone use validation	Method of tumor localization procedure
Austria		
Australia	Possible to obtain network data from the 3 providers in Australia.	Tumour localization protocol will be followed using Neuroradiologists.
Canada		
France	Data provided by operators	A Neuroradiologist expert for all French cases
Germany	Validation study based on operator data	Tumor localization study using common protocol
Greece	Contact with operators to investigate feasibility	Recruitment of neuroradiologist for tumor localization validation is feasible, if this will be decided by the group
Israel		Neuropathologist in each center
Italy	Data provided by operators: still to be defined with them	Tumor localization study using common protocol
India	Validation study using common protocol. Possibly with operators, feasibility yet to be established	Tumor localization study using common protocol
Japan	Validation study	Not sure yet
New Zealand		
Spain	Validation study	Tumor localization study using common protocol
Taiwan		
Netherlands	Validation study based on operator data.	One or more neuroradiologists.

VII. Tumor Localization-

Owing to the expected low carcinogenic effect of radio-frequency radiation, the main objective of the MOBI-KIDS study will only be achieved if precise data are collected both on the exposure levels of all study subjects and on the diagnosis of cases. It is therefore proposed that an attempt will be made to establish a more precise location for the origin of the tumor. Relevant levels of exposure due to mobile phone use are received only in the immediate vicinity (within a few cm) of the handset and consist mainly of RF of the frequency of operation (around 450, 900, 1800 and 1900 MHz) of ELF in the 10-20 Hz range.

To this end, centers will attempt to locate diagnostic post-operative MRI or CT images for all cases. A neuro-radiologist will be asked to mark the tumor on specially developed grids which correspond to the planes used in neuro-radiology (sagittal, axial and coronal). The full protocol and instructions for neuro-radiologists can be found in Annex L. If images are not available, tumor localization may be done using surgical and/or radiological records following the recommendations studying the protocol.

Table 10 summarizes localization procedure by each center.

VIII Biological samples

It is preferable that all centers will try to collect biological samples from all study subjects. The biological samples will be stored in well protected tissue banks for future analysis within the planned case-control study. No commercial use will be made of this material. The samples will not be used for any purpose other than those listed in this protocol unless the appropriate ethical review committees have given their consent.

The following centers will collect blood samples:

The following centres will collect saliva samples:

- Spain
- Australia (Melbourne, Sydney and Perth centres)

DNA from collected saliva or blood samples will be extracted to study gene-environmental interactions in the risk of glioma and meningioma. The statistical power of the study by itself is low (power calculation conducted with Quanto http://hydra.usc.edu/gxe/), but will serve to generate hypothesis and, most importantly, to contribute to future international consortia on the aetiology of these rare tumours in young people.

Other samples:

- Spain will collect fingernail samples for evaluation of heavy metal exposures.

The protocol for DNA collection is detailed in Annex P.

IX. Exposure assessment

This part of the study aims to determine the distributions of the Specific energy Absorption Rate (SAR) from RF fields, ELF magnetic flux density and induced current density produced inside the head by hand-held phones, and to assess the extent to which any other sources may contribute materially to exposure.

Development of an exposure gradient for RF and ELF

The main goal of the exposure assessment project will be to develop an exposure gradient such that each subject in the case-control study is allocated an exposure index.

In the absence of clear and consistent data from laboratory or animal studies, there is no clear indication of the most appropriate physical quantity to be related to possible long term health effects of RF and ELF electromagnetic fields produced from mobile phones.

In the case of the RF fields, however, it would seem reasonable to quantify exposure in terms of the total energy absorbed by the user's body. This energy, in turn, depends on the duration of exposure and on the SAR (Specific energy Absorption Rate), i.e., the amount of energy absorbed per second per unit mass of tissue. The duration and frequency of phone calls can be deduced

from the interview or operator(s) data. However, the power absorbed by the body depends on several factors such as the phone technology (e.g. GSM, DECT, UMTS, WiFi), the location of the phone during usage (e.g. laterality) and the function performed by the phone (e.g. calls, messaging). The importance of all of these factors will be investigated.

Extensive studies have been carried out to numerically and experimentally characterize the exposure to RF sources in terms of SAR. Experimental tools and protocols have been developed for standards, such as IEC 62209 or CENELEC 50361 (homogeneous phantoms). In recent years, the exposure in non-homogeneous adult heads has been analyzed and numerical studies have also been performed to assess the exposure of children.

Because of the limited availability of child head models in the past, studies were performed with children's head models that were based on adult heads, using a non-uniform downsizing (morphing). This approach is limited due to the fact that morphing inadequately accounts for the age dependence of the internal anatomy and variability between individuals. Thus, current comparisons between SAR induced in adults and children are difficult to generalize as the differences observed could be due to this inaccuracy. Recently MRI-based child head models have become available, leading to improvements in the dosimetry.

In the case of ELF electromagnetic fields, exposure is usually quantified inside the body in terms of induced current density. This quantity depends on the strength and frequency of the electromagnetic field, and is also likely to depend on the phone technology and the mode of operation. Induced current density rises broadly in proportion with frequency and this provides a basis for summing exposures at different frequencies. However, biological sensitivity is also an issue. For short-term health effects, i.e. stimulation effects, sensitivity of the central nervous system (CNS) decreases with increasing frequency, but it is unclear whether such an assumption should be made for long-term health effects such as cancer, given the lack of an established mechanism. The exposure assessment group will make a judgment on how to proceed in this respect.

ELF magnetic flux densities from GSM phones are highly non-uniform and have a high harmonic content. Magnetic flux densities fields are typically less than 30 μT at the surface of the phone, diminishing rapidly with increasing distance. Large, sensitive coil-based probes have been used to capture the waveform and spectra; however, measurements with these probes at distances less than around 10 cm are difficult to interpret because of the high variability of these fields within the volume of the sensor. Smaller Hall-effect probes and fluxgate magnetometers have been used to map the magnetic flux density to within 5 mm of the phones, but either their bandwidth is not large enough to fully capture the waveform, or the noise of the instrument will only allow mapping of the fundamental component.

Numerical simulations of current densities induced in the body due to ELF fields from GSM mobile phones as well as simulations of the source have been developed in recent years. Finite element methods (FEM) and finite integration techniques (FIT) for whole-body calculations have been used to take into account the non-homogeneity of tissues. Values of 3.6% and 4.1% of the ICNIRP basic restriction were found for the FEM and FIT model respectively, which imply maximum current densities in the CNS of 72 μA m^{-2} and 82 μA m^{-2} respectively.

Work conducted to date is limited, however, and additional work is needed using larger, more representative samples of GSM digital mobile phones and phones of non-GSM types such as DECT, WiFi and UMTS. The use of commercially available miniature Hall-effect sensors seems to be the most promising approach to measurements for the future.

RF exposure assessments from other sources

There are many RF sources that people may be exposed to and which may contribute materially to RF exposure of tissues inside the head. Such sources will be considered in this study. The objective will be to analyze the exposure induced by sources not in immediate proximity to the body, but possibly in the same room, such as WiFi access points and DECT base stations, as well as sources in the wider environment such as broadcast radio transmitters and mobile phone base stations. The brain exposure will be estimated using FDTD to simulate whole-body exposure to plane waves. Numerically, the exposure to waves coming from multiple directions will be estimated and the brain exposure analyzed.

ELF exposure assessments from other sources

Although the main interest in the study is exposure from phones held close to the head, other ELF sources in the environment must be considered as well since they may give rise to comparable induced current densities in the head. These sources will be identified in the development of the questionnaire and more detailed exposure assessments for these sources will be conducted in order for them to be included, where appropriate, into an exposure gradient.

Sources in the environment generally operate at the power frequencies (50/60 Hz) and the fields usually arise as an unintended consequence of the use of electricity.

There have been many studies of exposure to ELF magnetic fields arising from the distribution and use of electricity at power frequencies. Studies have been conducted to investigate particular sources and to quantify personal exposure in epidemiological studies. Given the large amount of existing material, including reviews, this part of the project will mainly involve consideration of results in the literature. For the older subjects in the study, it may also be important to consider occupational ELF sources.

Development of Gridmaster head cartographies

Methods have been developed during the course of INTERPHONE to produce a generic spatial distribution representative of RF exposure in adults using mobile phones. Using an anatomical 3-D atlas of the brain, neuroradiologists try to identify the probable location of origin and the contour of the tumor from MR and CT images. This atlas is known as the Gridmaster and the RF SAR in each cube of 1 cm side was estimated for phones operating in different frequency bands and used on different sides of the head.

The SAR values in Gridmaster cells for INTERPHONE were developed from experimentally measured compliance testing data for a range of mobile phones. In the proposed study, computer modeling will be used to assign values to the Gridmaster cells for ELF and RF exposure from different types of HMPs and from plane waves/uniform fields at the frequencies of common environmental sources. France Telecom has head models derived from MRI scans of children of various ages (from 5 to 15 years old) and these will be available for the project. Based on the Gridmaster atlas, the voxels in these child head models that are associated with a given Gridmaster cell will be identified and indices assigned to them. A mapping of the head voxels into the Gridmaster will then be conducted to derive average SAR and induced current density values within each Gridmaster cell.

Exposure gradient tool-kit

A set of instructions will be prepared for the epidemiologists so they can calculate exposure values. The sources of information are:

- The questionnaire – This will identify the types of phone that have been used and which sides of the head they have been used against. It will also provide information about any other sources of exposure to be considered, and durations and frequencies of exposure.
- The Gridmaster databases – The reported tumor location will have to be referred to the relevant Gridmaster exposure databases to determine the exposure values. The contributions from a range of sources will then have to be summed in an appropriate way.

Exposure assessment for other occupational or environmental factors

Several environmental and occupational agents have been suggested as being associated with brain tumors among children and adults. Among them: parental smoking, home and occupational exposure to pesticides and use of hair dyes and sprays. In addition dietary n-nitrous compounds have been linked to the disease as well. Interestingly, little is known about specific risk factors for brain tumors in adolescence, which falls in between the two age groups that have been studied most extensively. It is therefore of importance to collect detailed information on environmental/occupational exposures over life, starting in uterus and into adolescence. Detailed information on parental occupational history, residential history, day-care attendance history, occupational history including side-jobs and holiday jobs will be collected. Environmental exposures will be estimated based on questionnaire responses and via linkage with GIS databases on environmental exposures, where available. Parental occupational and exposures due to side-jobs and holiday jobs will be estimated via linkage with existing job–exposure matrices.

X. Analyses

Analyses will be carried out in parallel at the region/country level by the national study investigator and internationally at CREAL. The detailed protocol for the main data analysis (for mobile communication devices) will be prepared in advance (no later than April 2011) and agreed by all centers. The main analysis will include data from all centers and will be published centrally. No partial combined analysis of the main analysis will be published prior to the main combined publications.

The use of the national data set is the prerogative of the national investigators.
Any group within the collaboration can propose any additional analyses, in the form of short proposal sent to CREAL which will circulate it to all PI's. Each center will be free to participate or not.

Briefly, the main analysis will be based on conditional logistic regression for matched sets using STATA. If study centers use a frequency-matched rather than an individually matched design in the data collection phase, controls will be matched to cases post hoc, chosen from among those who fit the matching criteria, to have been interviewed as close as possible to the case (this is important because mobile phone use among children is expected to continue increasing during the study period and delays between case and control interviews could be a source of bias in the risk estimates). **The reference date** for calculating exposure will be set to the date of the diagnosis of the case in each matched set. Similarly, in analyses using tumor localization, exposure of the controls will be estimated at the location of the tumor of their matched case.

Analyses will be conducted for all brain tumor types combined, as well as, where numbers of subjects allow, for different tumor types and for malignant and benign tumors' separately.

The study will use two main approaches to characterize exposures from use of mobile phones:

- Exposure derived from mobile phone history: The responses to the questionnaire will provide detailed information on historical patterns of mobile phone use. This information will allow the computation of relevant indices of exposure such as cumulative call time, average call duration and cumulative number of voice calls without hands-free devices, overall and within specific time-windows.
- RF and ELF exposure: the distribution of RF and ELF exposure in the head varies according to a number of factors (see WP4), including the age of the subject (and consequently the size and location of the relevant anatomical structures), type of telephone and network (frequency and type of transmission: digital or analogue, continuous or discontinuous, use of power control), as well as the actual patterns of use of the phone. We will use the algorithms developed in WP4 to assess exposure (and related uncertainties) to RF and ELF for each study subject. Separate assessments will be made for mobile phones and for other sources.

All exposure variables, except time since first exposure, will be truncated to 1 year before the reference date. Cumulative number and duration of calls will be analyzed as categorical variables (based on deciles of the distribution of these variables among controls who were regular users) excluding use with hands-free devices and excluding data calls.

The effects of age, sex and region will be taken into account systematically in the conditional logistic regression, and all analyses will be adjusted for educational level of the parents (as an a priori surrogate for socio-economic status). A priori, we do not have strong grounds for believing that the other possible risk factors for brain tumours on which information will be collected (such as family history of brain tumour, past medical radiation exposure) would be related to mobile phone use. Nonetheless, the possibility of confounding by these factors will be examined empirically and they will be included in risk models where their inclusion results in a change in the ORs for the mobile phone use variables of 10% or more.

Separate analyses for each region will also be carried out and formal tests for heterogeneity of risk will be performed. Explanations of inconsistencies between regions will be sought through detailed examination of available information on study design and exposure. Unless strong heterogeneity is found which can be explained by differences in methods or levels of exposure, results of combined analyses will be presented.

Information will be collected by questionnaire on a number of potential risk factors for brain tumours in children, adolescents and young adults. These include the subject and his/her family's history of diseases, contact with other children, contact with animals, factors during pregnancy and delivery, ionising radiation exposure and exposure to other environmental and occupational risk factors. Analyses will be conducted to evaluate whether these factors are in fact related to risk of brain tumours in children, adolescents and young adults and, if so, whether they might confound or modify the possible association between brain tumour risk and RF/ELF exposure.

Statistical power

About 750 cases of brain tumours are expected every year among participating countries. Data collection is planned for two and a half to three years, with a total of about 1 450 cases in the European part of the study and 1 900 overall (including about 380 benign tumours). Table 11

shows the magnitude of the odds ratio (OR), that could be detected, with 80% power, based an assumed alpha level of 0.05, two controls per case and complete recruitment and participation of cases. Power calculations are shown in the table for different scenarios of exposure. Although the current prevalence of exposure (percentage of the population using mobile phones) in the study populations is higher than those shown in the table, the scenarios chosen are based on lower prevalences, reflecting use 7 or more years in the past, when, if there is a risk, we would expect the exposures of aetiological relevance to have occurred (see discussion of latency p.9). Thus, under the assumption that about 10% of the subjects have used mobile phones 7 years or more in the past, the study would have enough statistical power to detect increased risks of around 30%.

Table 11 – Size of the Odds Ratio that can be identified under different scenarios with 80 % power

Prevalence of exposure (5-10 years in the past)	**Number of cases** (2 controls per case)		**OR** that could be identified
20%	1 455	European component	1.25
	1 929	Entire study	1.21
10%	1 455	European component	1.33
	1 929	Entire study	1.28
5%	1 455	European component	1.47
	1 929	Entire study	1.40

When the disease being studied is not common, such as CNS tumors in young ages, increasing the number of participating countries and enrolment of more than one control per case are the only ways to increase statistical power. While the importance of enrolling two controls per case and of incorporating centers outside Europe may not be obvious in the above calculations, they become essential for analyses of subgroups of tumors. Because RF energy absorption in the brain is very localized, the effect, if any, may be restricted to a small part of the total brain, of the order of one quarter or less of the brain tissue. It is therefore important that sufficient power is available to study such effects which would then be apparent only in a subgroup of cases, of the order of 300 or 400. A subgroup of 300 cases would correspond to 20% of the total number of cases in the European study and 15% in a study including non-European centres. The gain of enrolling 2 controls per case in a study of a subgroup of 300 cases would result in having the power to detect an OR of 1.8 compared to an OR of 2.0 if only 1 control per case was enrolled.

It should be noted that any power calculation is only indicative, since it is very difficult to evaluate, a priori, the effects of missing values, misclassification, lower then 100% recruitment and confounding. It is for this reason that a very high power is proposed since the study should be able to detect even a very low increased risk. No power calculations are presented for interactions including gene-environment interactions since these do not form part of the proposed study. Such interactions will be considered only if a main effect of the environmental exposure (mobiles) can be documented.

XI. ORGANIZATION OF THE STUDY

A. Study period-

Three phases are foreseen:

- The first phase was started in March 2009 and includes study organization.
- The second phase will be started between July 2010 and July 2011, depending on the country (date related to obtainment of ethics approvals and necessary funding) will cover a period of 2.5 years and will include data collection.
- The last year of the study (1/3/2013-28/2/2014) will be devoted to data analysis.

Table 7 summarizes the study period for each centre.

B. List of work packages

Table 12: The MOBI-KIDS project includes seven complementary work packages

WP	Institute	PERSON MONTH	Tasks beyond the EU contract
WP1: Scientific coordination and conduct of the epidemiological study. This WP includes two separate but complementary activities: the overall scientific coordination of the project, which will last throughout the entire duration of the project, and the conduct of the epidemiological study in all participating countries.	**CREAL**	**87**	
	FIMIM	0	
	UU	34	
	FT	0	
	HPA	0	
	LMU	65	
	MUVI	24	
	UNITO	36	
	ARECEA	53	
	UOA-SARG	18	
	GERTNER INSTITUTE	27	
	UOTTAWA	38	
	MONASH	49	
	AUCKLANDUNI	18	
WP2: Finalization of the study instruments These include the core protocol and the different questionnaires that will be used for data abstraction, which will be used in all countries, information material for study subjects, the procedures for implementing the study, which will have to be adapted to take into account the specific logistic and legal constraints in each of the participating countries, while	CREAL	10	
	FIMIM	0	
	UU	3	
	FT	1	
	HPA	2	
	LMU	3	
	MUVI	3	
	UNITO	3	

WP	Institute	PERSON MONTH	Tasks beyond the EU contract
maintaining consistency and uniformity of data collection, information material for subjects etc. The analysis protocol will also be developed.	ARECEA	3	
	UOA-SARG	3	
	GERTNER INSTITUTE	**20**	
	UOTTAWA	3	
	MONASH	3	
	AUCKLANDUNI	3	

WP	CENTER	PERSON MONTH	Tasks beyond the EU contract
WP3: Quality assurance This includes ensuring quality of the procedures in place for the conduct of the study, validation of the questionnaire, quality control of the data collected, quality assessment and validation of the exposure estimates, verification of diagnoses and verification of tumor localization by neuroradiologists. Formal analyses will also provide insight into the resulting uncertainty of the study outcome.	CREAL	4	
	FIMIM	0	
	UU	**20**	
	FT	0	
	HPA	0	
	LMU	3	
	MUVI	3	
	UNITO	3	
	ARECEA	3	
	UOA-SARG	3	
	GERTNER INSTITUTE	6	
	UOTTAWA	3	
	MONASH	3	
	AUCKLANDUNI	3	
WP4: Exposure assessment To determine the distributions of the Specific energy Absorption Rate (SAR) from RF fields, ELF magnetic flux density and induced current density produced inside the head by hand-held phones, and to assess the extent to which any other sources may contribute materially to exposure.	CREAL	10	
	FIMIM	0	
	UU	8	
	FT	7	
	HPA	**15**	
	LMU	0	
	MUVI	0	
	UNITO	0	
	UOA-SARG	0	
	GERTNER INSTITUTE	0	

WP	CENTER	PERSON MONTH	Tasks beyond the EU contract
	UOTTAWA	0	
	MONASH	5	
	AUCKLANDUNI	0	

WP	CENTER	PERSON MONTH	Tasks beyond the EU contract
WP5: Data analysis and management This WP includes the setting up and maintenance of databases, programming of validation tools and of exposure indices, the analyses of the validation studies, of the non-response questionnaires as well as the main analyses of the relation between the risk of brain tumors and exposures to RF and ELF from mobile phones and other relevant and important sources of exposure in the general environment of young people. This WP will rely on the results of WP1 (the conduct of the case-control study) and WP4 (the estimation of exposure for each of the subjects in the study).	**CREAL**	**25**	
	FIMIM	0	
	UU	8	
	FT	0	
	HPA	2	
	LMU	5	
	MUVI	5	
	UNITO	5	
	ARECEA	5	
	UOA-SARG	5	
	GERTNER INSTITUTE	5	
	UOTTAWA	5	
	MONASH	5	
	AUCKLANDUNI	5	
WP6: Dissemination This WP includes the development of the project communication action plan and tools, the scientific publications arising from the study as well as dissemination activities aimed at the effective information of the public and public health and other stakeholders.	CREAL	3	
	FIMIM	10	
	UU	2	
	FT	1	
	HPA	1	
	LMU	**20**	
	MUVI	2	
	UNITO	2	
	ARECEA	2	
	UOA-SARG	2	
	GERTNER INSTITUTE	2	
	UOTTAWA	2	
	MONASH	2	
	AUCKLANDUNI	2	

WP	CENTER	PERSON MONTH	Tasks beyond the EU contract
WP7: Project management This WP will support the Scientific Coordination in the follow-up of the workplan and in Consortium management issues. It will deal with financial, administrative and legal aspects of the project, with special emphasis in workplan monitoring, promotion of efficient communication among participants and reporting processes.	CREAL	2	
	FIMIM	**28**	
	UU	1	
	FT	0	
	HPA	1	
	LMU	1	
	MUVI	0	
	UNITO	0	
	ARECEA	0	
	UOA-SARG	0	
	GERTNER INSTITUTE	1	
	UOTTAWA	0	
	MONASH	0	
	AUCKLANDUNI	0	

C. Subcommittees

Epidemiological subcommittee (EpiSub):
A body which will advise and work on the study design, data collection and analyses issues. It will include 4-5 persons, including epidemiologists involved in data collection and analysis and 1-2 experts in exposure assessment involved in WP4.
The Epidemiological subcommittee has been set up at the outset of the project. Its initial membership will be composed of , , (partner 3), (partner 6) , (partner 5) and (partner 11) (the WP leaders) and (Partner 7). Its main goals will be advising on the questionnaire, the design of the study and the data collection issues. Once the data collection phase has started, the EpiSub will monitor progress and difficulties, assist in problem resolution and plan the detailed analyses protocols. This body will meet at least twice per year during the first four years and once in the fifth year and decision making procedures will follow the same mechanisms as in the General Assembly.
The composition of the EpiSub may change during the course of the project lifetime, in the event of resignation or departure of any of its members, or if the scope of the work to be carried out warrants a change of expertise at the level of the Project Board. In such event, the departing members will be replaced within the EpiSub by members appointed by the General Assembly.

Exposure assessment subcommittee (EASub):
A team that will advise on exposure assessment related issues during the project. It will include 4-5 persons, including the leaders of the exposure assessment tasks in WP4, and 1-2 epidemiologists from WP1 and WP5. This subcommittee has been set up at the outset of the project. Its initial membership will consist at first of the main partners in WP4: ,

and (respectively Partners 5, 4, 3, 14 and 1). It will advise on the information to be collected by questionnaire and from network operators. It will also give recommendations on the development of RF and ELF exposure gradients and, towards the end of the study, in the application of the gradient and interpretation of the results of the analyses of risk in relation to these exposures.
The EASub will meet at least twice per year during the first four years and once in the fifth year and decision making procedures will follow the same mechanisms as in the General Assembly. Both the EpiSub and the EASub meetings will be held in conjunction with the General Assembly meetings when feasible.
The composition of the EASub may change during the course of the project lifetime, in the event of resignation or departure of any of its members, or if the scope of the work to be carried out warrants a change of expertise at the level of the Project Board. In such event, the departing members will be replaced within the EASub by members appointed by the General Assembly

Ad-hoc committees/task groups:
Consultative committees and task groups assisting the Project Board for scientific and technical matters – this will include a committee/panel of pathologists, one of neuroradiologists, a questionnaire task-group. Ad-hoc committees, and task groups with consultative functions, will be formed as needed during the project, so that the expertise and knowledge necessary to assist the SC on scientific and technical grounds are gathered. Independent external experts will be asked to sign an agreement to ensure confidentiality. It is foreseen that a committee of pathologists will be constituted to review the diagnosis of a sample of the cases, and a committee of neuroradiologists to review the localization of tumors. The members of these committees will be selectively determined during the project's development depending on the issues to be discussed.

D. Co-ordination

General assembly (GA):

A body gathering all partners participating in the project, with decision-making responsibility in matters affecting the overall project strategy, composition of the consortium and budget allocation between work packages. The General Assembly will be chaired by . It will be a decision-making body dealing with issues affecting all participants and/or the project as a whole, such as overall strategy. It will approve, before the start of the project (via the Consortium Agreement), the management structure, and the decision-making principles and responsibilities of all management bodies as described in this section. It will also have the right to propose amendments to such structure as the project progresses. Typically, the General Assembly will deal with amendments to the work plan, changes in the composition of the Consortium and budget allocation between work packages.
For decision-making purposes, each partner in the project will have one representative and one vote in the General Assembly. General Assembly members will be required to have the authority to make decisions on behalf of their respective organizations, or clarify the relevant line management. Two thirds of the project partners attending a General Assembly meeting will constitute a quorum. Simple majority of the attendants will be sufficient for decision adoption, except in those cases when a unanimous decision is required by the Commission procedures, the Study Protocol or the Consortium Agreement. In the event of a tied vote, (as chair) will have an additional vote. General Assembly meetings will be held once a year, so that the project evolution and governance are visible and transparent for all participants, and contributions are timely gathered and discussed. A

representative of DG Sanco will be invited to attend part of the General Assembly meeting (where non-confidential issues are discussed).

Project board:

The Project board is an executive body, comprising senior representatives of each work package leaders, including , which will act as the project steering committee. It will advise the General Assembly on issues of technical development, work plan updates, and effort and budget re-assignment. The composition of the Project Board may change during the course of the project lifetime, in the event of resignation or departure of any of its members, or if the scope of the work to be carried out warrants a change of expertise at the level of the Project Board. In such event, the departing members will be replaced within the Project Board by members appointed by the General Assembly.
Project Board members will have the authority to take corrective actions as necessary within their respective organizations, or clarify the relevant line management. The Project Board will be an executive body responsible for decisions regarding the project development, which cannot be operatively taken in the framework of a general forum, or decisions that must be dynamically and swiftly made to avoid endangering project objectives. In particular, changes in the work plan and resource allocation within work packages (at the proposal of any of its members) will be a prerogative of the Project Board. It will also be able to make recommendations regarding any other project issue, including evolution of the partnership composition. The Project Board will also monitor and review progress, ensure that objectives are met and approve deliverables. For these purposes, the Project Board will meet at least every three months, either face-to-face or via internet or teleconferences. Project Board members might be assisted by technical or managerial staff from their organizations for these meetings. The Project Board will be allowed to require specific actions or reports from and/or Work Package Leaders s in order to solve any issues that cannot be clarified or agreed at a lower level. These include in particular the resolution of disputes and matters relating to allocation of funding, as well as situations in which the project efficiency might be endangered. At the initiative of any of its members, the Project Board will also be able to constitute committees for matters that require specific attention (such as ethics), and to establish working procedures for such committees. For decision purposes, each member of the Project Board will be allocated one vote. Two thirds of the participants attending a meeting of the Project Board will constitute a quorum. Simple majority of the attendants will be enough for decision adoption, except in those cases when a unanimous decision is required by the Study Protocol or the Consortium Agreement. In the event of a tied vote, (as chair) will have an additional vote. In all of its activities, the Project Board will be assisted by any committees created for specific purposes.

Scientific co-ordination (SciC):

The Scientific co-ordination will have a key role in global scientific leadership, quality assurance policy and assessment of the project (Partner 1). As Chair of the General Assembly, , CREAL) will be responsible for the overall scientific leadership of the project. will provide strategic guidance, devise changes in scoping and focus of the different tasks, co-ordinate all efforts of Work Package Leaders and manage dependencies between tasks, linking the project components towards a successful completion. will be a central figure for conflict resolution, decision-making enabling and consensus building, supported by . will also coordinate the participation of ad-hoc Committees as needed, and be in charge of promoting the definition of high quality standards applicable throughout the work plan, directing the efforts towards assessment and validation of the project, and supervising overall ethical principles.

Project management (PM):

A management team set up by FIMIM for daily management of the project (Partner 2) with . The project management team will follow-up activities and monitor compliance with the work plan, planned resources and time schedule. It will also provide close support to the scientific coordination, including appropriate liaison with the European Commission. The Project Management will also support WP leaders in day-to-day management, promoting synergy and efficiency throughout. It will facilitate communication among partners, ensuring timely delivery of the project deliverables and tracking milestone achievements.

The Project Management will also be in charge of risk management (identification, assessment of potential problems and opportunities, mitigation and contingency plans), and will manage quality control procedures on deliverables. It will deal with management of partnership (accession of new partners, withdrawal, relationships with external collaborators), grant agreement and consortium agreement (amendments, subcontracts, third parties) and other legal issues. It will closely co-operate with the Scientific co-ordination and Work Package Leaders in periodic reporting. The Project Management will be responsible for overall financial management (cost control of costs and justification, budget management, payments), supporting the SC in budget re-arrangements, and coordinating and supporting all partners in financial and administrative tasks. Finally, it will support the organization of meetings and the production of the corresponding minutes. For the development of these tasks, the Project Management office will initially benefit from the involvement of who will dynamically contribute to the project as the need arises. Other roles may be added according to the needs of the project regarding specific issues.

Leading participants of each work package.

Each work package is the responsibility of one participant, who will act as work package leader. The Work Package Leaders s will have responsibility for day-to-day management and co-ordination of the activities included in their respective work packages. Work Package Leaders will co-ordinate the implementation of the work package activities as defined in the work plan, implement solutions for problems, produce the corresponding deliverables, identify risks as early as possible and follow them up, and report to the Scientific co-ordination and Project Management the progress achieved against that planned. They will be able to raise proposals to the General Assembly regarding effort and budget redistribution, and re-assignment of roles and responsibilities, within their respective WPs.

Communication and conflict resolution

The management structure of MOBI-KIDS has also been designed to help secure both communication and conflict resolution procedures. As regards to communication, a Consortium communication policy will be established by , making extensive use of the web conference tool, including regular conference calls. A password protected intranet structure will be set up to support management activities, communication and exchange of information among participants. Online forms for progress reporting will be set up. An appropriate periodicity of face-to-face meetings will be established, so that it helps to propel efforts by friendly peer-pressure. Participants will be encouraged to hold work package, task or topic specific meetings as necessary for the implementation of the work.

Regarding conflict resolution, the project organization is devised to support a bottom-up approach. Conflicts amongst participants in any given activity will be solved at the work package level with the help of the respective Work Package Leader; if unresolved or in case of conflict of interest, the issue will be raised up to the level of and

Scientific co-ordination, who will use mediation and their expert and referent powers to objectively solve the issue. If still unresolved, the issue will in turn be referred to the General Assembly, where voting mechanisms take place. These procedures will be formally agreed upon in the Consortium Agreement. In cases where legal action is needed, the Project Management will seek to obtain the required authorization from the Consortium and act accordingly in agreement with the legal documents regulating the development of the project.
General management structure:
The management structure, which will be confirmed in the consortium agreement, will be integrated so as to promote smooth and dynamic collaboration between the project participants. The General Assembly will be the main decision body in the management structure, supported by the Scientific co-ordination / [redacted] tandem, which will steer the project in direct connection with Work Package Leaders for day-to-day activities. In general, Work Package Leaders will be leading the implementation of the different activities in their respective WPs directly in connection with involved partners, so there is no further organizational level corresponding to activity leadership per se.

E. Use of data

A common database will be developed for the questionnaire in this study, including a set of routine validations. Additional databases will also be set-up as follows: a follow-up database (including information on all cases and controls who were approached about participation of the study, whether or not they agreed to participate, reasons for non-participation if appropriate, and status of completion of data and sample collection); a database of non-response questionnaires; a data base for the phone use validation study; a clinical database, a database of tumor localization and a mobile phone database.

The use of the combined data is the prerogative of the Study Group. The use of each local or national data set is the prerogative of local or national investigators.

Access to the combined data set for further analyses may be provided to a local or national investigator or a third party for a well-described and specified purpose, only if written consent is obtained from all Study Group members. Analyses by such third parties will be performed in collaboration with the Study Group, and the interpretation of results will be discussed before any result is published. Such analyses will be permitted only if they do not pre-empt or duplicate work to be done by the Study Group.

Communication tools:

A study webpage was designed using the content management system "Drupal". The website provides information for the public as well as an internal area for the project members. The public area of the webpage contains different sections. In the "News" sections new content and changes are announced (as for example the press releases), a "Frequently Asked Questions" section offers basic information about the rationale and the concept of the study as well as background information about brain tumours in young people. Moreover, all collaborating centres are listed and each partner institute has a specific site, were visitors find local contact information as well as a short project description in the language of the respective partner country. Therefore, the different partner institutes contributed a translation of the project description. Altogether, the public zone of the webpage offers various information about the project.

The internal area is password-protected and accessible only for project members. Here various files can be downloaded, as for example general documents (e.g. the Grant

Agreement and Annexes), different versions of the study logo, templates for reports to the EC, deliverables already submitted to the EC, meetings information etc. Furthermore, a forum offers the possibility for internal communication and discussions and in a "Revisions" section files and documents can be uploaded, discussed and revised before they are submitted to the public.

In addition to the webpage, a web conference tool should be implemented enabling fast and efficient information and data exchange within the consortium. A web conference tool offers the possibility to discuss current issues emerging during the course of the project in the whole consortium. Moreover, it should be made possible not only to discuss project related issues live, but also to perform presentations online and to exchange and revise documents.

To achieve these goals, Skype was implemented as web conference tool. Skype enables telephone calls, instant messaging, file transfer and video as well as audio conferencing. Skype audio conferences currently support up to 25 people at one time, including the host. Furthermore, Skype provides the possibility to send files of any size as there is no restriction to the size of the document. The fact that Skype has become the largest international voice carrier indicates that it is a well approved and broadly accredited means of international communication.

F. Publications

A specific detailed protocol for the generation of high-quality scientific publications will be established. The protocol will include review and authorship policies.

The group will early on define a list of publications and presentation at scientific conferences in order to spread the knowledge about the project within the scientific community. The publications will be jointly authored by the participating investigators. Upon completion of the WPs, their findings shall be published by the group of investigators involved in each work package. The Consortium may at its discretion, but in accordance with the study protocols, publish methods and results of the work under the project in scientific symposia, scientific or research journals etc. Until the findings of the work packages are published, they will remain strictly confidential between the members of Consortium. However, representatives of concerned organizations (as may be deemed appropriate by Consortium) shall be informed of the results seven days before publication in confidence and in a co-coordinated fashion, with prior agreement of the publisher.

The participants in each work package will collaboratively work in the papers' design and writing and be listed as authors of these papers. A specific protocol for the generation of high-quality scientific publications will be established. The protocol will include review and authorship policies. All participants are expected to contribute to this activity coordinated by Partners 2 and 6. All participants will make their best efforts to ensure that all papers are electronically available through "open access" publications and/or an online directory, in accordance with Article 39 of the contract.

G. Financial aspects

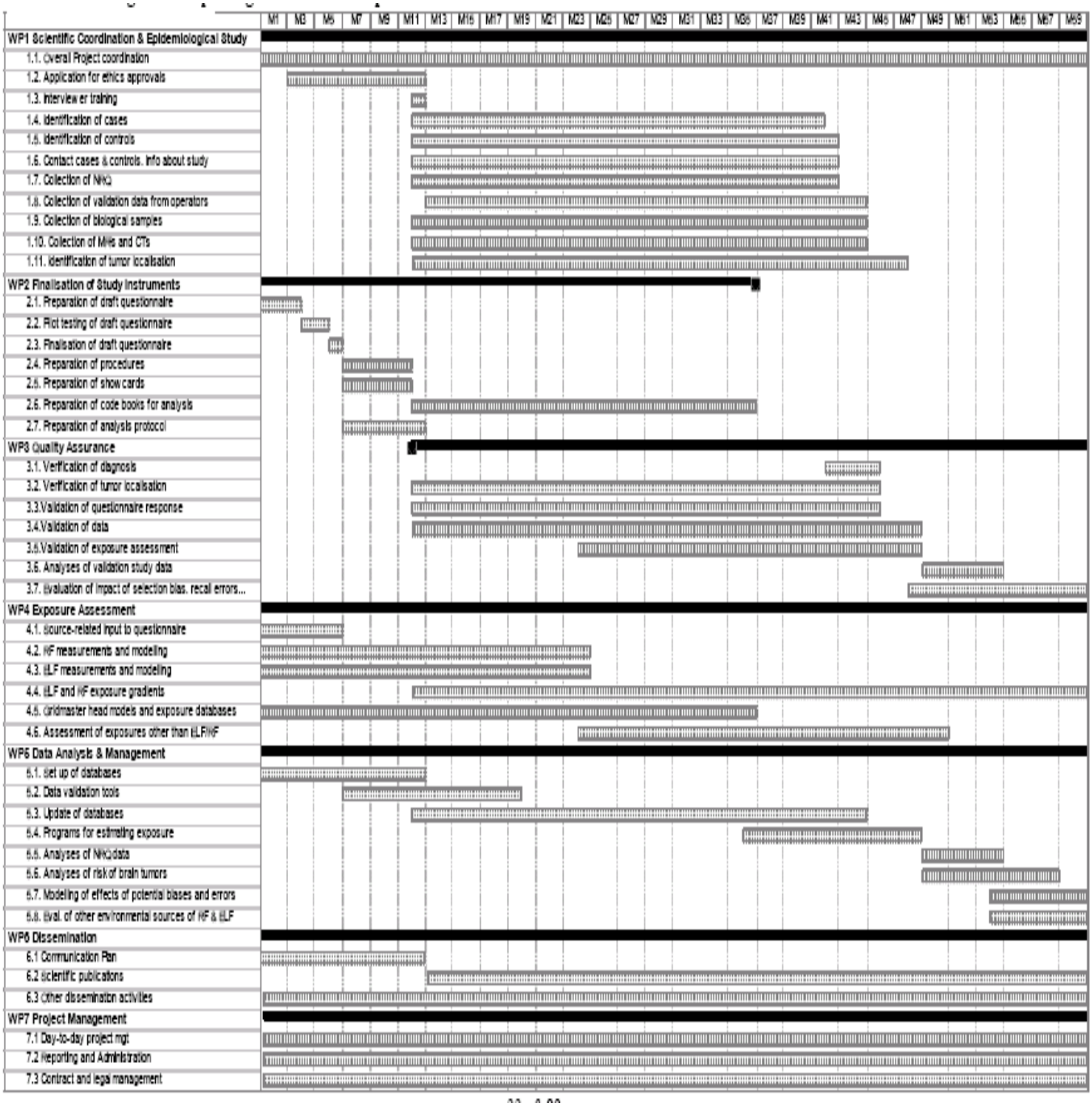
The financial plan for MOBI-KIDS builds on heavy involvement of expert personnel on each of the participating institutions, for a total effort of 775 person-months (pm). To ensure maximum efficiency, efforts in the work plan have been carefully adjusted on the work

package and activity levels, using several instances of a Responsibility Assignment Matrix (RAM).
Personnel costs have been calculated by asking each partner to estimate a faithful average PM cost, weighted according to the different types of personnel to be involved in the work, according also to each institution's policy. These results in a total personnel budget of 3 137 150 Euro.
It is important to mention that three of the participants, Partners 12-14 will participate in the project without EU funding. They plan to apply to local calls in their respective countries to cover part of the costs related to the project.
Aside from committing the 2 231 640 Euro not covered by the EC contribution with own resources, the Consortium will also contribute numerous other assets to the project in terms of: specific equipment and software licenses, plus other resources such as: computer network facilities; technical support personnel; server/hardware maintenance; database software; etc., to mention only the most significant.

Other local resources used in this project are detailed in Annex A.

XII. TIME TABLE

Timing of work packages and their components



XIII. ANNEXES:

Annex A: Financial sources by study centre

Annex B: List of eligible Brain tumor topologies and morphologies

Annex C: Country specific procedures for informed consent.

Annex D: Documentation of participation and refusal status

Annex E: Refusal questionnaire

Annex F: Guidelines for interviewing

Annex G: Questionnaires

Annex H: Details for communications

Annex I: Site specific questions

Annex J: Glossary

Annex K: Clinical questionnaire

Annex L: Protocol for localization procedure

Annex M: Protocol for validation of brain tumor diagnosis

Annex N: Protocol for validation of mobile phone use

Annex O: Protocol for validation of the questionnaire data

Annex P: Protocol for DNA collection