ESBACE Protocol
Section 1 Outline of Study and instructions for participating countries.

Background Literature

Epilepsy is one of the most common neurological conditions in the world, affecting an estimated 65 million persons worldwide (Ngugi et al 2010). The impact is substantial, with epilepsy contributing almost eight million disability-adjusted life years (DALYs), equivalent to 0.5%, to the total global burden of disease (World Health Organisation, 2008). The burden is particularly evident for those with severe epilepsy who were allocated the 4th highest disability weighting of 220 unique health conditions examined in the Global Burden of Disease study; a weighting surpassed only by individuals with severe multiple sclerosis, acute schizophrenia and persons with untreated spinal cord neck lesion (Salomon et al, 2012).

Prevalence estimates of epilepsy are, however, problematic (Ngugi et al 2010). In developed countries, evidence suggests that the prevalence of active epilepsy varies widely between 2.3-10.3 per 1,000 persons (Ngugi et al 2010). Epidemiological data are unavailable for many worldwide jurisdictions, and where available, differ widely in definitions and methodology (Kotsopoulos et al., 2002; Kotsopoulos et al., 2005). Particular disparities have arisen in the estimation and interpretation of prevalence estimates within Europe. A joint report by the World Health Organisation (WHO) and the Joint Task Force of the International League against Epilepsy (ILAE) and the International Bureau of Epilepsy (IBE) estimated six million individuals within Europe have epilepsy, with an associated per annum cost over €20 million (Epilepsy in the WHO European, 2010; Cross, 2011). These data are taken from a companion publication 'Atlas, Epilepsy Care in the World' which estimated the prevalence of epilepsy in Europe at 8.2 per 1,000 population (World Health Organisation, 2005). The authors note that this estimate is based on key informants in different countries and that the *'possibility remains of the data being incomplete and in certain areas even inaccurate'* (p.8).

Other data, enumerated from systematic reviews conducted under the auspices of the European Brain Council, provide estimates for the burden of brain disorders across 28 European countries in 2005 and again in 2010. In 2005, 2.69 million adults aged 18-65 years were estimated to have epilepsy in Europe, with an associated annual cost of €15.5 million (Andlin-Sobocki et al 2005). Updated data, published in 2010, observed a decline in both the numbers of individuals with epilepsy to 2.64 million, and the associated costs to €13.8 million. The authors propose that greater variation in costs, notably a reduction in reported prevalence from studies conducted in Italy and France contributed to the overall decline (Gustavsson et al 2011). The finding of a reduced number of people with epilepsy may be deemed unexpected given the ageing profile in Europe; a high risk group for epilepsy (Brodie & Kwan, 2005). In addition, the 34 prevalence studies employed in the European Brain Council calculations reveal considerable variation, both between and within countries throughout Europe. Prevalence estimates from seven studies conducted in Italy, for example, report a doubling of estimates from the lowest (3.0 per 1,000 reported by Gallitto et al 2005) to the highest (6.2 per 1,000 reported by Granieri et al 1983).

The cause of heterogeneity among epidemiological studies has traditionally been explained as a consequence of varying methodology (e.g. non-standardised screening tools) and differences in definition, diagnosis and classification (Leonardi & Ustan, 2002). More recently, evidence suggests that these factors have less influence on estimates, while the development level of countries, the age of study participants, and the study size have been identified as significant contributors to the observed variation among prevalence estimates (Ngugi et al 2010). Variation is also observed among studies estimating the cost of epilepsy. This variable pattern is thought to reflect methodological differences regarding cost elements considered, populations studied, and data sources used to derive the estimates (Begley & Durgin, 2015). Greater accuracy in estimates of the economic cost of epilepsy is required to equitably allocate resources and plan effective treatment.

In light of the varying estimates of prevalence and associated cost of epilepsy throughout Europe, and given the substantive impact of this condition, it is timely that a standardised pan-European study be conducted across representative regions throughout Europe to reflect differing levels of economic and health care development. These data will be of use to policy makers and service providers in planning equitable and targeted supports for persons with epilepsy in Europe.

Overall aims of the European Study on the Burden and Care of Epilepsy (ESBACE)

ESBACE is a European Commission funded project that aims to provide standardised data on the burden of epilepsy throughout Europe. Specifically, ESBACE aims to determine the prevalence of epilepsy and explore its impact in representative regions of four European countries; Austria, Denmark, Ireland and Romania. Individuals with epilepsy and a control group comprising individuals who do not have epilepsy, matched on basic demographics, will be recruited to a 12 month follow up to determine the impact of epilepsy as measured by cost, quality of life and stigma. National registers will also be used to estimate prevalence in two of these countries, Denmark and Ireland, to determine the level of association between bottom-up population-based estimates and top-down register-based estimates. The project will also conduct an audit of pathways to care for individuals with epilepsy within these jurisdictions to identify models of best practice and areas for improvement. More broadly throughout Europe, a survey of national epilepsy support organisations will collate information on current epilepsy care and resources. In combination, these data aim to provide standardised data on the prevalence and impact of epilepsy throughout representative regions of Europe, and to explore more broadly the level of service provision currently supporting individuals with epilepsy in Europe.

Methodology

Identifying a case study region:

Within each of the four participating countries, a representative region with clearly defined boundaries and population of around 50,000 will be selected as the study region. Accurate population data (broken down by age and gender at a minimum) must be available on the region for use as a denominator in determining prevalence. It is desirable that the region selected for the study should be reasonably representative of the country; consequently data (broken down by age and gender at a minimum) for the region and for the whole country will be required.

In Ireland, for example, the study region is an area known as Balbriggan. Full details on the 57,427 persons living in Balbriggan are available from a national census conducted by the Central Statistics Office, the state body responsible for compiling national statistics. The statistics produced by the Central Statistics Office permit a comparison of the demographic profile of people living in Balbriggan with the full Irish population. Research teams in Austria, Denmark and Romania will need to identify a source that can provide comparable data (broken down by age and gender at a minimum) between their region and the full national population.

Determining if a person lives in the study region:

There are two steps in the process of determining if a potential participant lives in the study region:
(1) Determine if the person's address is located in the region
(2) If the address is located in the study region, determine if the person is 'usually resident' in the region

(1) Determining if the person's address is located in the region:
All potential participants will have to have their address unambiguously located, and a definite and rapid decision made as to whether it is located in the study region or not. To locate a residence within the study region, each research team will need to:

- access regional maps and clearly outline the boundaries of the study region
- identify the location of every potential participant's address on the regional map
- include all persons in the study whose address is located within the region
- exclude all persons in the study whose address is located outside the region

Appendix A (at the end of this document) provides an example of how the address of each potential participant in Ireland will be assessed as being located in Balbriggan, the study region for Ireland. The Irish Central Statistics Office define Balbriggan as having the following boundaries: Balbriggan (Urban), Balbriggan (Rural), Ballyboghill, Balscadden, Clonmethan, Garristown, Hollywood, Holmpatrick, Lusk, Rusk or Skerries. An online tool developed by the Central Statistics Office allows users to enter an address to verify if it is located within the region. ***Research teams in Austria, Denmark and Romania will need to identify either paper-based or electronic mapping systems to make a determination on whether each potential participant's address is located within the study region.***

(2) If the address is located in the study region, determine if the person is 'usually resident' in the region

For most individuals, the address they provide will be that of their family home. In some cases, however, the address provided may suggest that the residence is not a family home (e.g. university accommodation, hospital, children's boarding school, disability service accommodation, prison, army barracks, etc.). In these cases, research teams need to make a determination on whether the person is 'usually resident' in the region. To make this determination, a precise and common definition of 'usual residence' must be adhered to by all research teams. The agreed operational definition for usual residence in ESBACE is a modified version of that employed by the US Census Residence Rule. Essentially, the US Census Residence Rule identifies people's usual residence as the place where they sleep 'most of the time'. Appendix B presents a determination on a variety of situations where a person's usual residence is ambiguous. ***The guidelines in Appendix B should be used by all research teams where ambiguity arises.***

Standardised case ascertainment methodology:
A standardised case ascertainment methodology will be employed whereby individuals are identified and invited to participate in ESBACE via healthcare providers (specifically, General Practitioners and hospitals) who provide services in the case study region. While research teams in some jurisdictions may be permitted to receive patient names from healthcare providers, and can therefore contact patients directly, this practice is not permissible in other countries due to data protection legislation. ***For this reason all participants will be approached by healthcare providers on behalf of the research teams in each country via a postal survey***.

In jurisdictions where patient lists may be forwarded to research teams, ethical approval should be sought to access these lists on the grounds that they may be used at a later stage of analysis to assess coverage and response rates. These patient lists should <u>not</u> be used by researchers to contact patients directly.

The standardised case ascertainment methodology prohibits the possibility of participants self-enrolling in the study. In the event that individuals with epilepsy present directly to the research team, they will be informed that they should contact their healthcare provider to determine if the provider is enrolled in the study. If the healthcare provider has not enrolled with the study, the individual cannot participate. Researchers should however record the sex and age of any individual presenting to self-enrol, despite the fact that these individuals cannot participate.

Incentivising participation:
Research teams in each country should consider local opportunities to encourage the participation of healthcare providers: examples may include hosting continual professional development seminars on epilepsy; exploring opportunities to gather data as part of audit studies, liaison with professional associations or advocacy groups etc. Any requirements in disclosing such activities to appropriate Research Ethics Committees must be considered.

Selection of case ascertainment sites within the study region:
Within each study region general practitioners and hospitals will be the primary case ascertainment sites for enrolment into the study. Discussion among research teams revealed that other common case ascertainment sites, such as EEG laboratories, are not present across all four jurisdictions and therefore cannot be approached. Research teams in each jurisdiction will need to ensure that individuals residing in communal facilities (e.g. Residential living options for persons with intellectual disability or elderly individuals) are captured within the data gathered from general practitioners and hospitals. Additional data collection may be required where a residential facility is deemed to fall beyond the scope of mainstream healthcare providers. Appropriate ethical approval must be sought from all case ascertainment sites in keeping with national and local practices in each jurisdiction.

Participating hospitals will comprise both paediatric and adult hospitals who deliver outpatient neurology support to patients with epilepsy living within the study region.

Participating General Practitioners (GPs) will comprise all primary care practices who serve persons living within the region. Data from the UK's Health & Social Care Information Centre (2013) indicates that the average patient list in the UK is 1,600 patients; as such approximately 32 GPs would typically serve a

population of 50,000. Recent figures from Ireland indicate identical numbers, where 64 GPs are employed per 100,000 population (Teljeur et al, 2014).

The number of participating hospitals and GPs will likely vary in each of the four participating countries as a reflection of differing patient list sizes. ***Research teams will comprise a listing of all eligible hospitals and GPs*** and will outline the justification for the selection of hospitals and GPs approached in their region.

Recruitment of case ascertainment sites within the study region and ethical approval:
Research teams in each jurisdiction will be responsible for ensuring that they have the necessary ethical approval to invite relevant hospitals and GPs to participate in this research. The documents presented in the Appendices to this protocol are based on the local requirements of University College Dublin's Research Ethics Committee. ***These documents should be considered as templates:*** research teams gathering data in other countries will need to consider amendments to accommodate local ethics committees' requirements.

Relevant hospitals and GPs will be approached by the research team in the first instance by letter inviting them to participate in the study. A copy of the draft correspondence issued to healthcare providers inviting them to participate in the study and outlining their responsibilities should they wish to take part is presented in a separate document (**Section 2; Materials for Healthcare Providers and Participants**). The correspondence for Healthcare Providers includes:

Appendix C: a letter of invitation to hospitals
Appendix D: an information sheet for hospitals
Appendix E: a letter of invitation to GPs
Appendix F: an information sheet for GPs
Appendix G: a consent sheet for GPs

Consent forms have not been provided for hospitals as, in Ireland, consent will comprise formal written approval from each hospital's research ethics committee. Research teams in other countries will need to determine if they require a consent form for hospitals. If so, the consent sheet for GPs presented in the appendices may be helpful as a template document.

Researchers in each participating country will need to consider for each case ascertainment site whether their initial approach to the hospital/GP is:
(1) to seek support in making a submission to a research ethics committee or
(2) to invite the hospital/GP to participate in ESBACE noting that research ethics has already been obtained by the research team as required.

In Ireland, for example, it is likely that the initial approach to hospitals will be item (1) above - to seek support in making a submission to a research ethics committee. Typically, a consultant level hospital employee is required to support any application for research ethical approval. In this instance the letter of invitation and information sheet will be sent to the relevant hospital consultant seeking support, and similar correspondence will be used to complete the research ethics application.

In Ireland, it is likely that the initial approach to GPs will be item (2) above - to invite the GP to participate in ESBACE noting research ethics has already been obtained by the research team as required. Template documents presented in the appendices will need to be amended accordingly by researchers in ESBACE depending on their local needs. It is imperative that data collection does not begin without the necessary research ethics approval being in place.

Once appropriate ethical approval is received, and each site has received a letter of invitation and information sheet, researchers should await contact by GPs and hospitals to determine their participation. If a hospital or GP has not been in contact within a 2-3 week period, researchers should contact them by phone to determine participation. Researchers should personally contact all identified hospitals and GPs serving the region to determine if they will or will not participate in ESBACE.

Hospitals/GPs who decline the request to distribute information to patients will be asked to provide summary information on the size of their service, and the numbers of persons in the study region who meet the study

inclusion criteria. This information would be highly valuable to the research team and given its anonymised summary nature, does not contravene data protection. Researchers should note in applications for ethical approval that ***sites who decline participation in the full study will be asked to provide summary anonymised data*** on the number of patients within the region reaching the inclusion criteria.

All Hospitals/GPs who have the required ethical approval and respond positively to the invitation to participate will be invited to discuss the research project in greater detail with a member of the research team by phone or face to face, whichever is most convenient. On receipt of a signed consent form and/or a statement of ethical approval, hospitals and GPs will be considered recruited to the study.

It is essential that a full list is kept by researchers of all hospitals and GPs who were issued an invitation to participate. A template sheet recording all contacts with hospital/GP is presented in **Appendix H Section 2; Materials for Healthcare Providers and Participants**.

Selection of participants sourced via GPs:
Each GP will be asked to identify all persons (both children and adult) reaching the inclusion criteria for the study (defined below). Parents/legal guardians will be approached for consent on behalf of all individuals deemed children (in Ireland 18 years or younger – research teams in other countries may need to amend) and persons under guardianship at the start of the study.

Inclusion criteria for children and adults recruited from GPs
Inclusion criteria

- Individuals who live in the study region
- Individuals with a diagnosis of epilepsy
- Individuals who have experienced a single unprovoked seizure

Exclusion criteria

- Individuals living outside the study region
- Individuals who do not have a diagnosis of epilepsy and have never experienced a single unprovoked seizure.

GPs will be asked to collate a listing of their patients who meet the inclusion criteria. While local practices will differ, researchers should provide a selection of search strategies GPs may use to identify patients depending on their resources (e.g. computerised patient list). Depending on local practices these search strategies could include:

(1) identifying eligible individuals using locally employed primary care administrative systems.

(2) identifying individuals using ICD 10 codes (more detail is provided in Appendix I) –

- G40.1-G40.9 Epilepsy;
- G41.0 – G41.2 and G41.8 to G41.9 Status Epilepticus;
- F80.3 Specific developmental disorders of speech and language (Landau-Kleffner syndrome);
- R56.8 Other and unspecified convulsions.

(3) identifying individuals who were or are prescribed AEDs for seizures (a generic list is provided in Appendix J.)

- Prior to distributing this list to GPs, researchers in each country are required to make the following amendments:
    - provide a list of brand names of all AEDs sold in their individual country
    - delete those drugs that are not sold in their jurisdiction (mindful some might be sold but not formally approved).

GPs will be asked to distribute by post a pre-prepared information pack to each person they identify. GPs will be asked to send a reminder pack within an approximate six week period to those who have not responded. In order to know who should receive a reminder pack, researchers will need to inform GPs which patients have

responded to the first wave of the survey. Patients will be informed in the information sheet that their GP will be made aware of whether or not they respond.

The following template letters of introduction, information sheets and consent forms are presented in the separate document **Section 2; Materials for Healthcare Providers and Participants.** Please note that these documents are based on the ethical requirements of University College Dublin. Research teams may find these documents of assistance, but it is likely that local ethical committees will require modifications.

Appendix K: a cover letter jointly signed by the GP and Principal Investigator in each country to patients reaching the inclusion criteria outlining the study and requesting patient participation.
Appendix L: an information sheet for patients reaching the inclusion criteria
Appendix M: a consent form for patients reaching the inclusion criteria or parents/guardians in the case of children and those under guardianship inclusive of a short form to gather contact details (e.g. address, phone, email) and details of their GP, consultant physician and neurological outpatient clinic.
: a small stamped addressed envelope for patients reaching the inclusion criteria to post their consent form and short form directly to the researchers.
Appendix N: a cover letter from the Principal Investigator in each country to control participants outlining the study and requesting participation.
Appendix O: an information sheet for control participants.
Appendix P: a consent form for control participants (parents/guardians as appropriate) inclusive of a short form to gather control participants' contact details (address, phone, email)
: a small stamped addressed envelope for control participants to return their consent form and short form directly to the researchers.

It is essential that the consent forms returned from each patient reaching the inclusion criteria can be:

- linked to the GP/hospital from which they were issued
- linked to the control consent form issued in the survey pack.

Researchers should use a numeric code to identify each GP/hospital and each participant and this code should appear on the consent form for both the participant reaching the inclusion criteria and the control recruited by this participant. The code should comprise a six digit number comprised of:

1. the first number should denote the country where the data is gathered (Austria =1; Denmark=2; Ireland =3; Romania =4)
2. the second number should denote if the consent form was issued by a GP=1 or by a hospital=2
3. the third and fourth number should denote which GP/hospital issued the consent form. Researchers will need to create two lists; one of all GPs and another of all hospitals. Researchers should list all GPs/hospitals alphabetically and then assign a number to each, starting with number 01.
4. the fifth and sixth number should denote the specific patient who is returning the form. Researchers will need to liaise carefully with GP/hospitals to ensure that the listing of patients held by GPs/hospitals corresponds to the numbering of issued consent forms. An alphabetical listing of patients should be drafted with each name assigned a number, starting with number 01.

Example, in a listing of 27 GPs covering the region in Ireland, GP 08 has 14 eligible patients reaching the inclusion criteria. Having listed all patients alphabetically, and correspondingly numbered, the 6th patient on the list (and the person's control survey pack) would be allocated the following code:
310806. In this way, a returned consent form from this participant and from his/her matched control can be identified.

Participants reaching the inclusion criteria will be invited to read the information sheet and consent form to inform them about the study. They will be asked to return the consent form (with contact details) to the researchers who will then contact them regarding participation. Participants will be invited to consent to the following key activities:

- to be contacted by the research team
- to be interviewed about their seizure(s) by phone or by face-to-face interview
- to permit the research team access their medical records to gather detail on their seizure status and treatment

- to permit neurologists and epileptologists review the summary data from their interview and medical records
- to enrol in a 12 month online follow up documenting their quality of life, stigma and costs

Once a consent form is received individuals are deemed to be enrolled in the study and their details should be forwarded to Aarhus University who will issue a confidential identification code.

Selection of participants sourced via hospitals:
A similar methodology will be employed in the selection of participants recruited through hospitals with outpatient neurology clinics that support the case study region. Clinics will be asked to identify all persons (both children and adult) reaching the inclusion criteria for the study (defined below). Parents/legal guardians will be approached for consent on behalf of children or those under guardianship the time of the study.

Note that the inclusion and exclusion criteria for hospitals are more specific than that used for GPs. The criteria for hospitals include a restriction for individuals seen within the clinic over a ten year period.

Inclusion criteria for patients with epilepsy recruited via outpatient neurology clinics
Inclusion criteria

- Individuals who live in the study region
- Individuals who have presented at the clinic since 1st January 2006 with a diagnosis of epilepsy or a single unprovoked seizure (including those whose diagnosis or single seizure occurred before 1st January 2016)

Exclusion criteria

- Individuals living outside the study region
- Individuals with a diagnosis of epilepsy or single unprovoked seizure who have not presented to the clinic since 1st January 2006.

Clinics will be asked to collate a listing of all patients meeting the inclusion criteria and distribute by post a pre-prepared information pack to each person. The survey pack will contain the same set of documents as that previously listed for GPs. Participants recruited via hospital clinics will be asked to consent to the same research activities as those outlined above for individuals recruited via GPs. In addition, all individuals will be invited to recruit a control participant as outlined previously.

Selection of control participants (at General Practitioner and Hospital sites):
Participants reaching the inclusion criteria will also be asked to forward an information letter, combined consent and contact detail form and stamped addressed envelope to one individual who is either a family member or friend matched for gender and similar age. The decision to recruit family or friends as controls was based on a combination of pragmatics across the four jurisdictions while acknowledging the advantages and disadvantages in the selection of all controls groups (Grimes & Schultz, 2006).

Participants with epilepsy/experience a single unprovoked seizure will be informed that family members/friends are being recruited as 'control' participants to allow researchers examine differences in quality of life, stigma and costs between people with epilepsy and people who do not have epilepsy.

Duplication
All participants reaching the inclusion criteria will be informed that they may be approached more than once to participate in the study; for example, a letter may be received from both the person's GP and from the person's outpatient neurology clinic. In such cases, the person should respond in full to the first invitation and respond to the second stating they have previously enrolled in the study. Researchers will need to keep a record of these duplications (see **Section 2; Materials for Healthcare Providers and Participants** Recording Sheet in Appendix H).

Recruitment to the study:
Once a consent form is returned, from a person with epilepsy or a control person, the person is considered recruited to the study and his/her details will be uploaded to a secure server hosted by Aarhus University (lead partner of ESBACE). Aarhus University will ensure that the storage of these enrolment data, and follow up survey data, are stored in keeping with best practice in data protection.

Data will be entered electronically via an encrypted internet access. Permission to store the data will be in accordance with local legislation (Austria, Ireland, Romania and Denmark) and the Danish Data Protection Agency (http://www.datatilsynet.dk/english/).

Each study centre (Austria, Ireland, Romania and Denmark) will keep a confidential list of participants' names, addresses and contact details with a corresponding study number issued by Aarhus University.

The study number will be used an identification key between the demographic and clinical data that will be entered anonymously to the secure server. No identifiable data (participants' names, addresses and contact details) will be shared between sites. These data will be retained for a ten year period.

To ensure the security of the data, the data storage will include:

- Security against theft
- Limited access (researchers only)
- Logging of all activities
- Blocking of repeated unauthorized logging attempts
- Updated software including firewall and antivirus
- Encrypted communication
- Routine test of the security system
- Full back of data
- Constant surveillance of data storage and security

Data collection tools for participants with epilepsy:
The following data collection tools will be completed by participants with epilepsy:

(1) Case Report Form for extracting data from medical records:

(2) Patient Interview Protocol:
To supplement the data from medical records, participants with epilepsy will complete a patient interview either in person or by phone, whichever is most convenient for the individual. The interview aims to provide additional information from which research teams may make a determination on the person's diagnosis. It is brief version of protocols developed by Prof Ruth Ottman and protocols developed by Prof Mike Kerr (with kind permission). The Patient Interview Protocol is presented in **Section 2; Materials for Healthcare Providers and Participants** Appendix R.

A Validation Process is required for these data:
(1) Intra-rater reliability – data from each individual extracting medical data will be checked for accuracy and consistency.

(2) Inter-rater reliability – in cases where more than one researcher is extracting data from medical records a sample of records should be reviewed a second time by a co-reviewer to determine the level of inter-rater reliability. To correct any areas of high disagreement, a higher percentage of reviews should be conducted earlier in the data extraction process (Brookes et al 2012)

(3) Validation by epileptologists – each Case Ascertainment Form and Patient Interview Protocol will be reviewed by epileptologists on the research team to make a determination on their diagnosis. An algorithm will be provided guiding the determination of epilepsy.

(4) Validation by independent committee – each research team will be asked to send a selection of non-identifiable case report forms and interviews to an independent committee to make a determination on the individual's epilepsy status using the same algorithm as that provided in step 3.

It is important that research teams in each jurisdiction consider the clinical implications of identifying a potential misdiagnosis. Epileptologists in each jurisdiction must take responsibility for ensuring that any individual suspected of being misdiagnosed will, with the individual's consent, receive appropriate clinical support to secure an appropriate re-evaluation of the diagnosis in keeping with local practices. Misdiagnosis may occur at two levels; persons incorrectly diagnosed with epilepsy and persons with epilepsy incorrectly diagnosed with a particular epilepsy syndrome. Patients will be asked on their consent form to specify if they would like any further assessment to take place in the event a misdiagnosis is encountered.

Assessing error

No method of case ascertainment is perfect. Every method misses certain categories of patients, and is prone to different errors. For this reason great efforts must be made to estimate and eliminate possible sources of error, and to use any other possible methods to check the prevalence estimates derived.

The following steps should be taken:-

Non-participating service providers

Every effort must be made to ascertain two pieces of information:

(1) what is the size of their service

(2) how many persons with epilepsy/single unprovoked seizures attend their practice

Non-participating persons with epilepsy/single unprovoked seizures

The number of non-participating persons with epilepsy/single unprovoked seizures should be ascertained whenever possible from each service provider. Any additional data on the gender and age breakdown of this cohort is very helpful. Recall that researchers should note in applications for ethical approval that ***sites who decline participation in the full study will be asked to provide summary anonymised data.***

Assessing completeness of ascertainment

It is likely that some patients will be reported from more than one health care provider during the study. It is **imperative** that each such duplicate identification is recorded, on each occasion, and that the sequence of these identifications is correctly kept. This allows for a simple, but useful estimate of the completeness of ascertainment.

Data collection tools for participants with epilepsy and control participants:

As each participant with a diagnosis of epilepsy or a single unprovoked seizure is invited to nominate a control person, it is likely that these pairings will return consent forms at a similar time period. Having consented, additional data from patient interviews and from medical records will be required from participants with epilepsy or those who have experienced a single unprovoked seizure. The process of gathering data from individuals who may have epilepsy could take several weeks resulting in this individual and his/her control potentially completing Time One (T1) data on quality of life and costs at different time periods. This difference in time periods may be reflected in the data gathered if seasonal or other temporal issues arise. For this reason, both participants and control should be invited to complete quality of life and cost questionnaires following their consenting to the study. Data may be removed for analysis for any participant with epilepsy or single unprovoked seizures who is found not to have met the inclusion criteria for the study following validation.

Follow up data include information on (1) quality of life and stigma (2) costs. All protocols are required to be translated into local languages with the support of the local research teams.

(1) Quality of life and stigma questionnaires will be distributed to participants with epilepsy and control participants who are deemed ***adult*** in each participating country (the age limit on 'adulthood' differs). ***These Quality of Life questionnaires are administered twice; at the beginning and end of a 12 month period commencing when the individual has consented to participating in the study***.

(2) Cost questionnaires will be distributed to participants with epilepsy and control participants of all ages and will therefore be completed by ***adult participants or parent/guardians*** for children and those under guardianship. These questionnaires are also administered on two occasions; at the beginning and end of a 12 month period commencing when the individual has consented to participating in the study.

The methodology for the collection of these data is by direct entry from participants with epilepsy or single unprovoked seizures and controls using an online survey hosted on a secure server managed by Aarhus University (lead partner). These data will be electronically stored with guidance from DG SANTÉ and compliance with Data Protection legislation. This methodology acknowledges the high rates of home computers available to participants in Austria, Denmark and Ireland. Rates of home computers are lower in Romania and for this reason data collection by face-to-face interview with researchers and simultaneous electronic data entry may also occur in this jurisdiction. If required, face-to-face interviews may take place in other jurisdictions. Procedures for data entry, storage and retention have been presented previously.

The following questionnaires will be used to gather Quality of Life and Cost data and are presented in full in a separate document **Section 3; Quality of Life and Cost Questionnaires.**

Quality of Life questionnaires will be administered to **adults** with epilepsy/single unprovoked seizure (Appendix T to Appendix X) and **adult** controls (Appendix T and U). These questionnaires are not administered to children.

Appendix T: Hospital Anxiety & Depression Scale *(** attached but note copyright so should not be distributed beyond project**)*
Appendix U: SF36 *(** attached but note copyright so should not be distributed beyond project**)*
Appendix V: Liverpool Impact of Epilepsy Scale
Appendix W: Revised Stigma Scale
Appendix X: Aldencamp & Baker Neuropsychological Assessment Schedule

The following measures will be used to gather cost data:

A cost questionnaire will be administered to children and adults with epilepsy/single unprovoked seizures and controls.

Appendix Y: ESBACE Cost Questionnaire

Guidelines for the translation of these instruments using a 'forward backward' methodology recommended by Prof Gus Baker are presented in Appendix Y following the ESBACE Cost Questionnaire.

Research staff

Two research posts are funded by ESBACE in each of the four participating countries gathering prevalence, QOL and cost data. Additional tasks may include coordinating hospitals to gather data for the NASH element of the study. Given the scope of work to be completed, post-graduate level scholars in some jurisdictions will undertake research duties within the ESBACE project in partial fulfilment of their degree. These early stage career clinicians and researchers will benefit from the opportunity to work alongside established practitioners; equally, the project will benefit from additional staff. The contribution of research staff completing post-graduate studies should be noted as required in all ethical applications. Similarly any publications required by these students should be discussed with the ESBACE executive committee.

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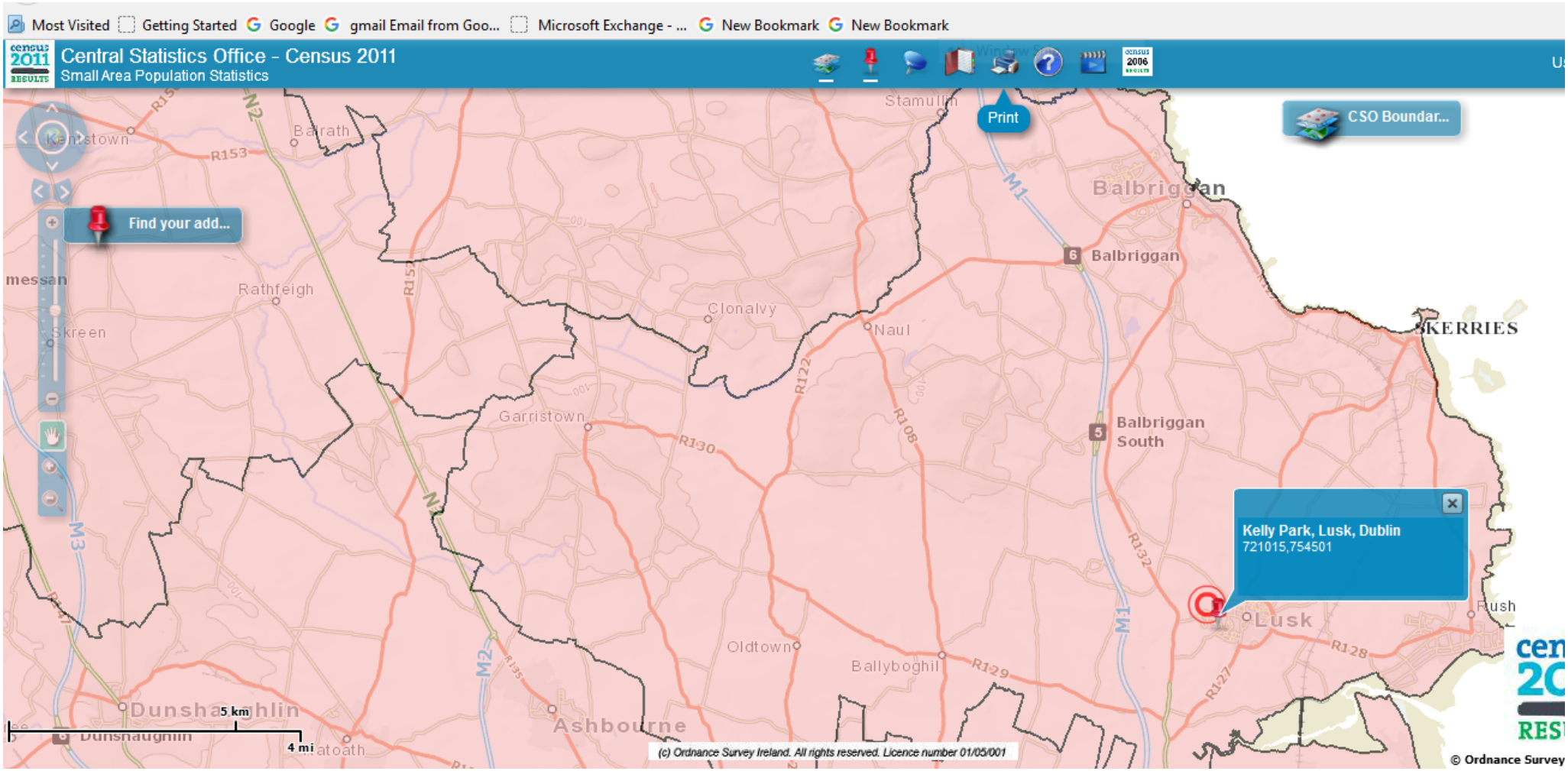
Appendix A:
Determination of Study Region

Each study team will be required to make a clear determination on whether or not each individual lives within the study region. To locate a residence within the study region, each research team will need to:

- access regional maps and clearly outline the boundaries of the study region
- identify the location of every potential participant's address on the regional map
- include all persons in the study whose address is located within the region
- exclude all persons in the study whose address is located outside the region

Each research team will need to record the local mapping system they use to validate a determination on whether the address falls within the study region.

Example of local mapping system used in Ireland:
In Ireland, the Central Statistics Office, the statutory body responsible for compiling Irish statistics, hosts a Small Area Population Statistics Mapping Tool. This online tool allows users to navigate to their location of interest by using an address search facility. Each individual address can be entered into the software and a visual representation of the location of the address will appear, as will the boundaries of the study region. In this way, a clear determination can be made on whether the address is within, or beyond, the geographical boundary of the region.


Most Visited
Getting Started
Google
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Microsoft Exchange - ...
New Bookmark
New Bookmark
Central Statistics Office - Census 2011
Small Area Population Statistics
Print
CSO Boundar...
Find your add...
Kelly Park, Lusk, Dublin
721015,754501
Balbriggan
Balbriggan
Balbriggan South
Lusk
Rathfeigh
Clonalvy
Naul
Garristown
Oldtown
Ballyboghil
Ashbourne
Skerries
Skreen
5 km
4 mi
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Appendix B:
Usual Residence

OECD define usual residence as 'the geographical place where the enumerated person usually resides'.

Applying the US Census Residence Rule, individuals should be included:

- at their usual residence, where they live and sleep most of the time
- at a facility/shelter if the individual (usually) lives with a group of other individuals
- at their residence on the day of case ascertainment in cases where a usual residence cannot be determined

Guidelines on Usual Residence

The general rule is that an individual is included in the prevalence figures if their usual residence, that is the location where they 'live and sleep most of the time', is within the study region.

PEOPLE AWAY FROM THEIR USUAL RESIDENCE AT CASE ASCERTAINMENT

People away from their usual residence at the time of case ascertainment, such as on a vacation or a business trip, visiting, traveling outside the country, or working elsewhere without a usual residence there (for example, as a truck driver or traveling salesperson) - Include these individuals if the location of the residence where they live and sleep most of the time is within the study region.

PEOPLE WHO LIVE IN MORE THAN ONE PLACE

People living away most of the time while working, such as people who live at a residence close to where they work and return regularly to another residence – Include these individuals if the location of the residence where they live and sleep most of the time is within the study region. If time is equally divided, or if usual residence cannot be determined, include these individuals if the location of the residence where they are staying at the time of case ascertainment is within the study region.

People who live at two or more residences (during the week, month, or year), such as people who travel seasonally between residences – Include these individuals if the location of the residence where they live and sleep most of the time is within the study region. If time is equally divided, or if usual residence cannot be determined, include these individuals if the location of the residence where they are staying at the time of case ascertainment is within the study region.

Children in shared custody or other arrangements who live at more than one residence – Include these children if the location of the residence where they live and sleep most of the time is within the study region. If time is equally divided, or if usual residence cannot be determined, include these individuals if the location of the residence where they are staying at the time of case ascertainment is within the study region.

PEOPLE WITHOUT A USUAL RESIDENCE

People who cannot determine a usual residence (e.g. homeless) **-** Include these individuals if the location of the residence where they live and sleep at the time of case ascertainment is within the study region.

STUDENTS

Boarding school students living away from their parental home while attending boarding school below the college level – Include these individuals if the location of their parental home is within the study region rather than the location of the boarding school.

College students living at their parental home while attending college - Include these individuals if the location of their parental home is within the study region rather than the location of the college.

College students living away from their parental home while attending college (living either on-campus or off-campus) - Include these individuals if the on-campus or off-campus residence where they live and sleep most of the time is within the study region.

College students living away from their parental home while attending college (living either on-campus or off-campus) but staying at their parental home while on break or vacation - Include these individuals if the on-campus or off-campus residence where they live and sleep most of the time is within the study region.

College students living outside their country while attending college outside their country These individuals are not included in the study.

Foreign students living in the country while attending college in the country (living either on-campus or off-campus) Include these individuals if the on-campus or off-campus residence where they live and sleep most of the time is within the study region.

PEOPLE IN ADULT PRISONS

People in prison on the time of case ascertainment Include these individuals if the prison is within the study region.

PEOPLE IN GROUP HOMES AND RESIDENTIAL TREATMENT CENTERS FOR ADULTS

People in group homes intended for adults - Include these individuals if the group home where they live and sleep most of the time is within the study region.

People in residential treatment centres for adults - Include these individuals if the location of the residence where they live and sleep at the time of case ascertainment is within the study region. If they do not have a residence where they live and sleep most of the time, include them if the facility is within the study region.

PEOPLE IN HEALTH CARE FACILITIES

Patients in general hospitals including newborn babies Include these individuals if the location of the residence where they live and sleep at the time of case ascertainment is within the study region. Newborn babies should be included if the residence where they will live and sleep most of the time is located within the study region.

People in hospitals/hospices who have no usual home elsewhere - Include these individuals if the location of the hospital is within the study region.

PEOPLE IN RESIDENTIAL SCHOOL-RELATED FACILITIES

People in college/university student housing - Include these individuals if the location of the college/university is within the study region.

People in residential schools for people with disabilities - Include these individuals if the location of the residential school is within the study region.

PEOPLE IN RELIGIOUS-RELATED RESIDENTIAL FACILITIES

People in religious group quarters such as convents and monasteries - Include these individuals if the location of the religious facility is within the study region.