Case-Control Study - Tobacco Overview of Risk (C-TOR)

C-TOR Study Protocol

Version 1.9
26 September 2005

PROPRIETARY AND CONFIDENTIAL

SIGNATURE PAGE

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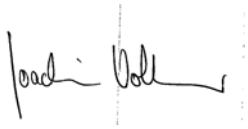

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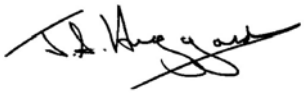

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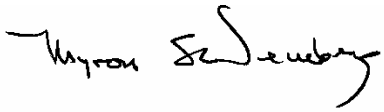

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Case-Control Study - Tobacco Overview of Risk (C-TOR)

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Version 1.9
26 September 2005

Sponsor:

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PROTOCOL SYNOPSIS

Title of study	Case-Control Study - Tobacco Overview of Risk (C-TOR)
Study background	It is widely accepted that smoking causes lung cancer and it is believed that tar content is a major risk factor. The response has been to develop lower-delivery cigarettes that emit lower tar, carbon monoxide and nicotine as measured by the standard ISO 'smoking machine' method. Studies have been conducted examining the risk of lung cancer from smoking so-called low tar (LT) products. The machine-measured yields for these LT products are typically in the order of 60% to 70% of traditional full flavor (FF) products. Data from these studies have been contradictory, with some stating decreased risk of lung cancer and others not. To date, no study has been conducted to evaluate the changes in risk of lung cancer associated with ultra-low tar (ULT, defined for the purposes of this study as 3 mg or less tar per stick) cigarettes. These ULT products have machine measured tar yields which are typically 10% to 30% of FF products and have had a significant usage in certain countries for the last 8 to 12 years. This time period (8 to 12 years) has been shown in smoking cessation studies to cause significant health benefits for former smokers, with a reduction in risk of developing lung cancer of potentially 50% of someone who continues to smoke FF products. Market data indicate that in certain countries there is a sizeable group of smokers who have 8 or more years of usage of ULT products. Considering the significantly lower yield of ULT products and the potential for a significant segment of the smoking population to have used these for at least 8 years, it is intended to compare the risk of developing lung cancer associated with the use of ULT and FF cigarettes.
Study objectives	**Primary objective** • To compare the risk of lung cancer of ULT (3 mg or less tar) and FF (10 mg or more tar) cigarette usage. **Secondary objectives** • To assess and model the impact associated with using cigarettes of different tar levels and other aspects of smoking on the risk of lung cancer. • To examine possible confounders and effect modifiers related to the primary hypothesis.
Study design	C-TOR is a non-interventional, multi-center, epidemiological case-control study in which relevant data about the diagnosis of lung cancer (cases) and the primary hospital admission diagnosis (controls) will be collected from hospital charts and physician information, and data about smoking history and other potential confounding or effect modifying issues will be collected using a questionnaire designed specifically for this study which is administered by a trained interviewer in the form of a computer-assisted personal interview (CAPI).
Study duration	It is planned that this data will be collected from December 2005 onwards for up to 36 months.

Study sponsor	The study sponsor is THE WEINBERG GROUP LLC, a Brussels based scientific consultancy. Philip Morris International is the sole financial sponsor of this study; however Philip Morris International has no active role in the design, analysis, conduct or dissemination of the study.
Study centers	Approximately 200 study sites in countries with sufficient market penetration of ULT cigarettes. These countries include Australia, Austria, Belgium, Finland, France, Germany, Greece, Hungary, Italy, Slovenia, Switzerland and the United Kingdom. Hospital sites with recently diagnosed primary lung cancer patients are eligible for participation (principal sites). For the identification and recruitment of control patients, the principal site as well as any other hospital site (satellite site) is eligible. Participating countries have been selected because market data indicate a relatively high use of ULT cigarettes for at least the last 8 years.
Sample size	It is anticipated that data will be collected on a total of 26,000 patients (cases and matched controls) to address the study objectives.
Indication/ Study population	Case patients with recently (not more than 90 days before execution of the informed consent) diagnosed, medically confirmed primary lung cancer and matching control patients with an admission diagnosis unassociated with smoking (for matching criteria see below). The lifetime smoking behavior has no impact on the eligibility of a patient and never smokers will also be eligible for the study.
Case patient population	Any adult with recently diagnosed confirmed primary lung cancer. ***Inclusion criteria*** • Age at least 18 years • Currently resident in one of the eligible countries • Medically confirmed primary lung cancer (ICD-10 codes for lung cancer: C34.0, C34.1, C34.2, C34.3, C34.8, C34.9) • Time interval between the date of diagnosis of lung cancer and the date of informed consent is 90 days or less • Signed informed consent form ***Exclusion criteria*** • Scores less than 18 on the Standardized Mini-Mental State Examination (SMMSE) cognitive test • Condition that would impair a patient's ability to participate in the interview • Diagnosis of mesothelioma (ICD-10 codes: D19.0, D19.1, D19.7) • Diagnosis of lung cancer secondary to another tumor • History of lung cancer prior to this incident diagnosis (i.e. previous lung cancer with recovery) • Previously included in the C-TOR Study as a case or control

Control patient population	At least one control per case, matched for age, gender, and administrative area of permanent residence. ***Inclusion criteria*** • Age at least 18 years • Currently resident in one of the eligible countries • Matchable to a case on: – Age within 5 years (i.e. ± 5 years to that of case) – Gender – Administrative area of residence 6 months prior to signing informed consent • Patient has one of the following admission/visit PRIMARY ICD-10 diagnoses: – Breast cancer (C50), prostate cancer (C61), carcinoma in situ or benign tumor of breast (D05, D24), carcinoma in situ or benign tumor of prostate (D07.5, D29.1) – Diseases of blood and blood forming organs (D50-D89) – Endocrine, nutritional, and metabolic disorders (E00-E90) except diabetes mellitus (E10-E14) – Diseases of the ear and mastoid process (H60-H95) – Appendicitis (K35-K37) – Cholelithiasis (K80) – Cholecystitis (K81) – Diseases of the skin and subcutaneous tissue (L00-L99) – Diseases of musculoskeletal system and connective tissue (M00-M99) except osteoporosis (M80-M82) – Diseases of genitourinary system (N00-N98) • Signed informed consent form ***Exclusion criteria*** • Scores less than 18 on the SMMSE cognitive test • Condition that would impair a patient's ability to participate in the interview • History of prior lung cancer • Previously included in the C-TOR Study as a case or control
Study procedures	Investigators will identify appropriate patients (cases and/or controls) at their sites. After the patient signs the informed consent, an interview will be scheduled. This private face-to-face CAPI will be performed by a trained interviewer and will last approximately 2 hours. Once the informed consent has been signed, the Investigator will complete the paper case report form (CRF). Additionally, he/she will try to match the case with a control from the same site according to the matching criteria. If this is not possible during a given time frame of 2 months, other study sites will have the opportunity to provide a matching control patient. A web-based data entry system will be used for coordinating, collecting and reporting administrative data. Appropriate electronic data handling practices and requirements for maintenance of patient privacy as governed by international codes and as required by national and regional laws will be strictly adhered to.

Data source	Patient data will be collected from two different sources: **Life Event History Calendar (LEHC) Questionnaire** An interview, using a LEHC CAPI questionnaire (patent pending), will be the main data collection tool for obtaining the patient's historic smoking behavior. The LEHC is a validated state-of-the-art approach to data collection which uses life events to enhance recall. Before proceeding with the interview, cognitive capability to respond reliably to the questionnaire will be tested. Cases and controls scoring less than 18 on the SMMSE cognitive test will be administered the short version of the questionnaire. The questionnaire will be administered to both cases and controls in the same manner. The performance of the trained interviewers will be subject to monitoring for quality control purposes with appropriate feedback on performance being provided. **Medical records** Information will be transcribed from medical records by the Investigator onto paper CRFs. The following data will be extracted for cases and controls: • Primary diagnosis and manner determined (cases) or diagnosis for hospital admission (controls) • Date of diagnosis
Data Protection & Quality Assurance	The study protocol will meet all applicable requirements and be carried out in accordance with good epidemiological practices and good clinical practices where applicable, appropriate electronic data handling practices and requirements for maintenance of patient privacy as governed by international codes and as required by national and regional laws will be strictly adhered to.
Statistical analyses	The primary analysis will compare the risk of lung cancer of ULT (3 mg or less tar) and FF (10 mg or more tar) smokers across all study sites and countries. The statistical analyses will use a two-sided level of significance of 5%. The relationship among use of cigarettes of different tar content, duration of use of different tar content, amount smoked and the risk for lung cancer will be modeled including use of data from patients who have never smoked and who have ceased smoking. Covariate and subgroup analyses will also be performed to examine possible confounders and effect modifiers related to the primary objective. The data from the first 100 patients will be used to validate the CAPI, data transfer and other procedures. The data from the initial group (up to the point where 750 matched controls have been interviewed) will be used to validate the definition of cigarette use, review the overall sample size estimates, examine patterns of missing data and variability issues within and between study sites.
Publication policy	To submit the study for publication in a peer-reviewed journal irrespective of the outcome.

Signature of Investigator

By my signature on this document, I certify that I have carefully read this protocol and agree to execute the study described herein in accordance with the protocol, in accordance with good epidemiological practices and good clinical practices where applicable, and applicable regulatory requirements.

Name of Investigator (printed)	Signature of Investigator	Date

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LIST OF ABBREVIATIONS

CAPI	Computer-Assisted Personal Interview
CDA	Confidentiality Disclosure Agreement
CRF	Case Report Form
CRO	Clinical Research Organization
C-TOR	Case-Control Study - Tobacco Overview of Risk
DWS	Dynamic Web-based System
EU	European Union
Eurostat	Statistical Office of the European Communities
FF	Full Flavor
FTC	Federal Trade Commission
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ID	Identification
IEC	Independent Ethics Committee
ISCED	International Standard Classification of Education
ISO	International Organization for Standardization
LEHC	Life Event History Calendar
LT	Low Tar
NCI	National Cancer Institute, National Institute of Health of the US Department of Health and Human Services
NUTS	Nomenclature of Territorial Units for Statistics
PMI	Philip Morris International
PRA	PRA International
PRADM	PRA Data Management
SMMSE	Standardized Mini-Mental State Examination
SOP	Standard Operating Procedure
TWG	THE WEINBERG GROUP LLC
UK	United Kingdom
ULT	Ultra-Low Tar
US(A)	United States (of America)
WHO	World Health Organization

1 STUDY BACKGROUND AND RATIONALE

An increased risk of lung cancer among cigarette smokers was first suggested in epidemiological studies in the 1950s.[1,2,3,4] Since then, it has become widely accepted that smoking causes lung cancer[5] with the tar content of smoke being considered a major risk factor. As a response, there has been a progressive reduction in the tar yields of cigarettes (see box). This has occurred via reductions in the maximum yields of traditional full flavor (FF) products. These reductions in tar yields have taken place in Europe and the United States as well as elsewhere in the world. In the European Union, this trend has been legally enforced such that the maximum machine-measured tar ceiling was first set at 15 mg in 1992 and reduced to 12 mg in 1997.[6] The tar level was further reduced by additional legislation[7] to 10 mg as of January 1, 2004. A further development has been the marketing of products that have lower machine-measured tar yields relative to standard products. These have been called low tar (LT) products. Their relative tar yield has varied over time as has the tar yield of FF products. Historically, a LT product could have had a tar yield of 13 mg, while currently a low tar product is one with typically 6-8 mg.

Terminology surrounding the tar content of cigarettes

Due to the historic evolving nature of cigarettes, reduced yields products have gone by a variety of names including lights, ultra-lights, low tar (LT) and ultra-low tar (ULT). Non-reduced-tar products are normally referred to as full flavor (FF). These names are not standardized and have not been coded at a national or international level. In fact, they have meant different things at different times. Tar content is measured by a standardized, machine-based process, in accordance with International Organization for Standardization (ISO) or the essentially equivalent US Federal Trade Commission (FTC) standards, with a specified number of puffs of specified duration. However, actual smoking practices vary among individuals, so this idealized machine-measured yield is not likely to correspond to the actual tar intake of the individual smoker.

For the purposes of this study, the following products definitions are used:

- Full Flavor (FF) – ISO machine-measured tar yield of 10 mg or more
- Low Tar (LT) - ISO machine-measured tar yield of greater than 3 and less than 10 mg
- Ultra-Low Tar (ULT) - ISO machine-measured tar yield of 3 mg or less

The past 15 years has also seen the introduction of products with very low machine-measured tar yields of typically 1 to 3 mg. Because of their lower tar yields, these ultra-low tar (ULT) products offer the possibility to reduce the tar dose to between 10 to 30% of that of a FF product.

However, it is not possible to draw conclusions concerning the actual reduction in dose. Smoking practices vary greatly among smokers. It is also accepted that smokers can, by various means such as increasing the numbers of cigarettes smoked, inhaling more deeply and taking puffs more frequently, compensate for reduced yields after switching to reduced tar and nicotine cigarettes. Given this inability to correlate machine-measured tar yields with dose, yet recognizing that a product with the potential to deliver a significantly lower dose than hitherto has been available for up to 15 years, it was concluded that a study to examine the risk of ULT cigarette use is necessary.

An examination of market penetration data[8] shows that the use of these ULT products has varied greatly, with very low market uptake (typically 1%) in the US compared to more than 10% in some EU countries. ULTs also have a significant share of the Australian market. These data also indicate that there are a significant number of

smokers in a number of markets who have smoked ULT for 8 to 12 years. This time period corresponds to data on smoking cessation, which is the baseline against which to compare any study which examines a product that purports to deliver a significant reduction in tar dose. For a former smoker who quit some 8 to 12 years ago, it is expected that his/her risk of lung cancer would be in the order of 50% of that if he/she had continued smoking cigarettes.[9] Hence, it is felt that to carry out a study that has the potential to yield meaningful results, it would be beneficial to study smokers who have switched to ULT for a similar period.

Although it is considered a different endpoint, a recent study by Sauer et al[10] illustrates the benefits of considering cigarettes with tar levels that are significantly lower than those of FF products. This study examined the relationship between myocardial infarction (MI) and cigarette tar content. This study identified an approximately 50% reduction in MI risk associated with smoking low tar (4.4 ± 1.4 mg nominal yield) versus high tar (16.4 ± 2.0 mg nominal yield) cigarettes. In comparing their results with those of previous studies, the authors point out that, "Although prior investigations have failed to identify a clear difference in MI risk by cigarette yield, most of these studies were performed more than a decade ago, before low-tar cigarettes became popular, and therefore may have had limited ability to detect an effect of higher- versus lower-yield cigarettes."

It is now possible to examine products with a broader range of tar yields than hitherto examined. This is necessary because there has been conflicting data and views as to whether LT products have resulted in any reduction in lung cancer in the population. This debate has influenced the view as to the potential for ULT products to have an impact.

The results of a meta-analysis of 16 epidemiological studies comparing the relative risk of lung cancer in lower tar yield versus higher tar yield smokers showed a significant reduction in risk.[11] With a fair degree of consistency, 35 other studies indicated a reduction of risk in the order of 20-30% for smokers of lower tar as opposed to higher tar cigarettes.[12] However, the findings of Harris et al[13] do not support the comparative benefit of lower tar cigarettes, but do support a reduction in lung cancer risk when comparing risk of smoking filtered cigarettes versus non-filtered cigarettes. In the conduct of the studies cited, products with tar contents that correspond to ULT (3 mg or less tar) levels were not addressed.

In addition, a 2004 report by the United States (US) Surgeon General[5] discussed the harmful impact of smoking on nearly every organ in the body. One of the important conclusions in this report was that "changes in cigarettes that reduce machine yields of tar and nicotine have not had any clear benefits for public health." This was supported by a National Cancer Institute (NCI) monograph[14] which focused on the risks associated with smoking cigarettes with lower machine-measured yields of tar and nicotine. The main conclusion of this review was that the use of lower tar cigarettes has not significantly decreased disease risk. In fact, the monograph concluded that the use of such cigarettes might be partly responsible for a reported increase in lung cancer for long-term smokers who have switched to the low tar/nicotine brands. It should be noted that this increase was observed in the United States (American Cancer Society prospective studies, CPS-I (1959-1964) and CPS-II (1987-1992)[as cited in 14] whereas over the same period, a decline was observed in the

United Kingdom[11] and Australia[12], for example. The NCI monograph attempts to explain the upward trend in US lung cancer, in spite of the reduction in machine-measured yields, by pointing out that switching to lower tar delivery cigarettes frequently leads to "compensation." However, it is a matter of some debate whether the NCI monograph approach fully explains the difference between US and other country's lung cancer trends, although differing lifestyles have been suggested as a possible additional factor.

A review of the literature related to LT cigarettes leads to the conclusion that a well-conducted study of the risk of development of lung cancer associated with use of ULT cigarettes, as compared to the risk of development of lung cancer as a result of the use of FF cigarettes, would be beneficial in that it could assist in resolving some of the uncertainty in this important area. As, by now, there has been significant use of ULT cigarettes in Europe and other areas of the world, it appears that a case-control study could supply answers to the question of whether lowering the yield of constituents is associated with a reduction in health risk and development of disease, specifically lung cancer.

2 OBJECTIVES

The main objectives of the C-TOR Study are:

Primary objective:

- To compare the risk of lung cancer associated with the use of ULT (3 mg or less tar) or FF (10 mg or more tar) cigarettes. Stated as a null hypothesis, the primary objective of the study is to show that the risk of developing lung cancer associated with the use of ULT cigarettes will not differ from that associated with the use of FF cigarettes by 25% or more.

Secondary objectives:

- To assess and model the impact of tar levels, time of use of different tar levels, and amount smoked on the risk of lung cancer.
- To examine possible confounders and effect modifiers related to the primary hypothesis.

The C-TOR Publications and Presentations Committee will ultimately submit the results of the C-TOR Study for publication (see section 10.3 for details of publication policy).

3 STUDY DESIGN

Study Characteristics

The current protocol describes the Case-Control Study - Tobacco Overview of Risk (C-TOR) Study. The C-TOR Study is a non-interventional, multi-center, epidemiological case-control study designed to compare the risk of developing lung cancer associated with the use of ULT cigarettes and FF cigarettes. A secondary objective of the study is the modeling of the impact of using cigarettes with different tar levels, time of use of different tar levels, and amounts smoked, on the risk of lung cancer. The final data of the study will be made available through publication. It is

anticipated that data on a total of 26,000 patients (cases and matched controls) will be collected to address the study objectives. The study design has been developed in close collaboration with university-affiliated experts, Clinical Research Organizations (CROs) and commercial/academic organizations. To improve the accuracy of patient information, a life event history calendar (LEHC) computer-assisted personal interview (CAPI) questionnaire (patent pending) will be used in this study to collect information regarding disease risk as a function of smoking.

In principle, either a prospective or retrospective epidemiological study design could have been chosen to compare the lung cancer risk associated with ULT and FF cigarette use. In a prospective study, one follows a large cohort of individuals for many years, records smoking information, other relevant confounding or effect modifying factors, and morbidity and mortality on a continuing basis. This approach has several advantages, including the avoidance of recall bias and the ability to obtain data on morbidity and all causes of death, not just lung cancer. The disadvantage is that such a prospective study needs to run for a very long time before relevant effects can be observed. Compared to a prospective cohort study design, a retrospective case-control study requires fewer participants and can be conducted in a shorter timeframe. The principal disadvantage of a case-control study design for a study of the association of tobacco use and lung cancer is recall bias and validation of patient reported information. In this study, a LEHC CAPI questionnaire will be used to minimize recall bias and to improve accuracy of patient information.

Study Outline

Cases are patients with recently diagnosed and medically confirmed primary lung cancer and controls are hospitalized patients with an admission diagnosis unassociated with smoking. Although the study will focus on lung cancer in current and former ULT and FF cigarette smokers, never smokers will also be eligible for the study (see section 9.1.1 for definitions). Relevant data about the diagnosis of lung cancer (cases) and the primary hospital admission diagnosis (controls) will be collected from hospital charts and physician information, and data about smoking history and other potential confounding issues and effect modifiers will be collected via a trained interviewer-administered questionnaire designed specifically for this study. This face-to-face CAPI will be performed by a certified trained interviewer and will last approximately 2 hours. Once the informed consent has been signed, the Investigators will complete the paper case report form (CRF) (see section 7.3 for details). Additionally, they will try to match the case with a control from the same site according to the following matching criteria: age, gender and administrative area of residence (minimum 6 months prior, for details of administrative area by country see Appendix A; see section 5.2 for details of matching criteria and control selection). If this is not possible during a given timeframe of 2 months, other study sites will have the opportunity to provide a matching control patient. The control patients will also be administered the interview.

A Dynamic Web-based System (DWS) will be used during the C-TOR Study for coordinating, collecting and reporting administrative data (see section 7.1 for details).

Study Duration

Lung cancer cases and matched controls will be recruited over a period of up to 36 months or until data on a minimum of 26,000 patients have been collected.

Study Organization

The Data Oversight Committee, the Steering Committee and the Study Team are responsible for monitoring specific aspects of the C-TOR Study. However, the final responsibility for the conduct of this study is with the Sponsor and the Investigators. Various services and resources are provided by independent firms and academic institutions. The C-TOR Study Team is comprised of university-affiliated experts, Clinical Research Organizations (CROs) and commercial/academic organizations. For details see Appendix B.

Study Sponsor

THE WEINBERG GROUP LLC (TWG) of Brussels, Belgium has been retained by Philip Morris International (PMI) to be the C-TOR Study Sponsor. The C-TOR Study and all related activities are completely funded by PMI. However, the contractual agreement between TWG and PMI requires that TWG act independently of PMI and that PMI has no active involvement in the design, conduct, analysis or dissemination of the results of the C-TOR Study. If, in the course of the C-TOR Study, TWG relies on any advice from PMI, it is required to acknowledge this in all reports and publications related to the C-TOR Study.

4 STUDY SITES

4.1 Identification of Potential Sites

It is planned that approximately 200 study sites in countries with sufficient market penetration of ULT cigarettes may participate in the C-TOR Study. The countries with the appropriate level of market penetration include Australia, Austria, Belgium, Finland, France, Germany, Greece, Hungary, Italy, Slovenia, Switzerland and the United Kingdom. Participating countries have been selected because market data[8] indicate a relatively high use of ULT cigarettes for at least the last 8 years. Hospital sites with recently diagnosed primary lung cancer patients are eligible for participation (principal sites). Study sites will also be responsible for the identification of matched controls (see section 5.2 for details of matching and control selection). For the identification and recruitment of controls, the principal site as well as any other hospital or clinic site (satellite site) is eligible (see section 5.3.2).

In order to be eligible, study sites must be able to provide privacy for the interview (questionnaire administration) as well as the staff resources required for organizational purposes.

4.2 Recruitment of Sites

Potential C-TOR Study sites will receive a C-TOR Study protocol synopsis. After having signed a confidentiality disclosure agreement (CDA) the sites will receive a final protocol containing the paper questionnaire, the CRF and the informed consent form. If the Investigator is willing to participate in the study, the study monitor will

perform a Pre-Study Visit to confirm the eligibility of the site. Following confirmation of eligibility, all remaining study related details will be discussed with the site, and the site will be formally initiated for study participation.

Site details will be entered by the study monitor into the Monitor Data Entry Screen of the DWS. The system will confirm the investigator identification (ID) number assigned by the monitor.

The processes described will apply to both principal and satellite sites. Satellite sites will be treated as autonomous sites in the C-TOR Study.

5 STUDY POPULATION

The lifetime smoking behavior has no impact on the eligibility of a patient and never smokers will also be eligible for the study (see section 9.1.2 for definition).

Lung cancer and all other diagnoses mentioned in this protocol are classified by the appropriate International Classification of Diseases (ICD-10) code.[15]

At all sites, details of potential cases and controls will be recorded in a Screening Log (Appendix C). This paper spreadsheet will document data on the enrollment of patients into the study including reasons for non-enrollment, and allow analysis of enrollment response rates for cases and controls. Further details are given in section 6.4.

The withdrawal of study patients is discussed in section 10.12.

5.1 Selection of Cases

Cases will be defined as any adult with a recent medically confirmed diagnosis of primary lung cancer. Eligible histological types of lung cancer include non-small cell lung cancer (e.g. squamous cell cancer and adenocarcinoma) and small cell carcinoma (also known as oat cell cancer). Patients with mesothelioma will not be included in this study. Further, cases will be excluded from participation if they have lung cancer secondary to other tumors or a past history of lung cancer prior to this recent diagnosis. The diagnosis of primary lung cancer must have been made 90 days or less (incident case) before signing the informed consent form.

5.1.1 Inclusion Criteria for Cases

Patients who fulfill the following criteria will be eligible for inclusion in the study:

- Age at least 18 years
- Currently resident in one of the eligible countries (see section 4.1)
- Medically confirmed primary lung cancer (ICD-10 codes for lung cancer: C34.0, C34.1, C34.2, C34.3, C34.8, C34.9)
- Time interval between the date of diagnosis of lung cancer and the date of informed consent is 90 days or less
- Signed informed consent form

5.1.2 Exclusion Criteria for Cases

Patients who meet any of the following criteria will be excluded from the study:

- Scores less than 18 on the Standardized Mini-Mental State Examination (SMMSE) cognitive test[16]
- Condition that would impair a patient's ability to participate in the interview
- Diagnosis of mesothelioma (ICD-10 codes: D19.0, D19.1, D19.7)
- Diagnosis of lung cancer secondary to another tumor
- History of lung cancer prior to this incident diagnosis (i.e. previous lung cancer with recovery)
- Previously included in the C-TOR Study as a case or a control

Patients must not meet any of the exclusion criteria. However, the SMMSE cognitive test will be performed as part of the interview and will determine whether patients complete the entire questionnaire (see section 6.1.1). Patients who score less than 18 on the SMMSE cognitive test and do not complete the full questionnaire (i.e., introduction, SMMSE, life event history calendar and socio-economic questions) will have met one of the exclusion criteria. Cases scoring less than 18 on the SMMSE cognitive test will not be matched with a control.

5.2 Selection of Controls

5.2.1 Matching

Matching will be employed to ensure that the cases and controls are similar with respect to selected variables, and that controls are chosen efficiently.[17] The most efficient way for the sites to select controls is through a pair-matching process in which controls are chosen based on matching for each case.[18] Age (± 5 years), gender, and administrative area of residence (place lived for a minimum of 6 months prior to signing informed consent form; see Appendix A for details of administrative areas by country) have been chosen as matching variables, meaning that the cases and controls are required to have the same proportion of patients with each category of each variable. It is intended that one control per case be recruited and matched for each of those matching variables (see sections 5.2.4 and 5.2.5). It is expected that as far as possible the same trained interviewer will interview a matched set to help protect against any type of differential interviewer bias.[19]

5.2.2 Hospital-Based Controls

The C-TOR Study plans to utilize hospital-based controls. An important advantage to using hospital controls is that they should be comparable to cases with respect to quality of information, because they too have been ill.[20] It is key that the quality of information be similar for cases and controls and it is also important to identify a control group that represents the "background" general population prevalence of smoking. Therefore, this group of control patients should consist of individuals with a variety of different smoking-unrelated (i.e. condition is not known to have an increased or a decreased risk of occurrence with relation to cigarette smoking) admission diagnoses. Mantel and Haenszel acknowledge that 'such a variety will minimize the risk of falsely concluding that the exposure affects the risk of study disease when the effect of exposure is actually linked to the diagnosis from which the controls were drawn. This approach will also help to avoid the problem of failing to

detect an association of exposure because the study and control diseases are both related to it.'[21]

Controls will be chosen based on hospital admission diagnosis. If a potential control patient has one of the acceptable diagnoses (section 5.2.3) as a PRIMARY diagnosis for hospital admission, then the patient is eligible for study inclusion. These diagnoses were determined not to be associated with cigarette smoking either by the US Surgeon General's Report on the Health Consequences of Smoking 2004[5] or by the International Agency for Research on Cancer (IARC) Monograph 83 on Tobacco Smoking[22]. If more than one acceptable control is found to match a case, the control patient with the admission/visit date closest to identification date of the case should be selected for study inclusion.

5.2.3 Diseases for Control Patient Inclusion

The following conditions coded by ICD-10 are acceptable as PRIMARY hospital admission/visit diagnoses for control patient selection. No other ICD-10 conditions are acceptable for control cases.

Acceptable diseases for Control Inclusion

- Cancer
  - Breast cancer (C50)
  - Prostate cancer (C61)
  - Carcinoma in situ or benign tumor of breast (D05, D24)
  - Carcinoma in situ or benign tumor of prostate (D07.5, D29.1)
- Diseases of blood and blood forming organs (D50-D89)
- Endocrine, nutritional, and metabolic disorders (E00-E90) except diabetes mellitus (E10-E14)
- Diseases of the ear and mastoid process (H60-H95)
- Appendicitis (K35-K37)
- Cholelithiasis (K80)
- Cholecystitis (K81)
- Diseases of the skin and subcutaneous tissue (L00-L99)
- Diseases of musculoskeletal system and connective tissue (M00-M99) except osteoporosis (M80-M82)
- Diseases of genitourinary system (N00-N98)

5.2.4 Inclusion Criteria for Controls

Patients who fulfill the following criteria will be eligible for inclusion in the study as controls:

- Age at least 18 years
- Currently resident in one of the eligible countries (see section 4.1)
- Matchable to a case on:
  - Age within 5 years (i.e. ± 5 years to that of case)
  - Gender

  - Administrative area of residence 6 months prior to signing informed consent (see Appendix A, Country Administrative Areas for Matching)
- Patient has admission/visit PRIMARY ICD-10 diagnosis from acceptable inclusion list of diagnoses (listed in section 5.2.3)
- Signed informed consent form

5.2.5 Exclusion Criteria for Controls

Patients who meet any of the following criteria will be excluded:

- Patient scores of less than 18 on the SMMSE cognitive test
- Condition that would impair a patient's ability to participate in the interview
- History of prior lung cancer
- Previously included in the C-TOR Study as a case or a control

Patients must not meet any of the exclusion criteria. However, the SMMSE cognitive test will be performed as part of the interview and will determine whether patients complete the entire questionnaire (see section 6.1.1). Patients who score less than 18 on the SMMSE cognitive test will have met one of the exclusion criteria. Under these circumstances, another matched control for the case will be sought.

5.3 Patient Identification Process

5.3.1 Identification of Cases

Cases will be recruited by a lung-cancer-patient-treating physician (Investigator) based at either general hospitals or specialist clinics (principal sites). The Investigator (or a designated person, i.e. Co-Investigator, Sub-Investigator, Study Coordinator or a person to whom the Investigator has appropriately delegated responsibilities) will identify the cases with recently diagnosed medically confirmed primary lung cancer in accordance with the inclusion/exclusion criteria stated in sections 5.1.1 and 5.1.2, respectively. A flowchart of the case identification process is included in Appendix D.1.

The Investigator (or designated person) will document all potential cases in a Screening Log (Appendix C). This paper spreadsheet will allow documentation of date of identification, age and gender, current administrative area of residence, admission diagnosis (ICD-10) and the outcome of screening including reasons for non-participation (see section 6.4 for details of the Screening Log).

The Investigator (or designated person) will inform the patient about all aspects of the study that are relevant to the patient's decision to participate and discuss his/her willingness to participate. If the patient agrees and signs an informed consent form, the Investigator (or designated person) will enter case patient data (preliminary patient ID number, date of birth, gender, administrative area of residence (minimum 6 months prior to having signed the informed consent form) and date of informed consent) into the Patient Data Entry Screen of the DWS. The system will then provide the case patient ID number which will be used to identify the case on all subsequent documentation. The case ID number will be reported to the CROs using the DWS (see section 7.1 for further details of the DWS).

If the DWS is unavailable or if a site does not have Internet access, a fax-based back-up system will be set up to report case recruitment and track the case ID number. In this scenario, faxed data completed by Investigators will be sent to and entered into the DWS by the dedicated CRO. The system will confirm patient ID numbers, and confirmation faxes will be returned to the Investigator.

The Investigator or interviewer will schedule an appointment for the face-to-face CAPI and the interviewer will update the interview status in the DWS (date interview scheduled/performed, interview status, date CD sent to PRA Data Management (PRADM)).

Once the interview has been conducted and the case scored less than 18 on the SMMSE (see section 6.1), this patient will have met one of the exclusion criteria (see section 5.1.2) and will therefore not be considered a case. Under these circumstances another case will be sought. Only if the long questionnaire (life event history calendar and socio-economic questions) has been completed for a case, a matching control will be identified.

5.3.2 Identification of Controls

As far as possible, controls will be recruited from the same hospital (or other units of that hospital) as the cases. The Investigator (or designated person) will use the DWS to produce a Site Case/Control Detail Report with the data on the cases to identify the matching controls. In addition to the inclusion criteria and exclusion criteria (as stated in sections 5.2.4 and 5.2.5, respectively), the control must meet the matching criteria (i.e. must be from same administrative area of residence as the case (minimum 6 months prior to having signed the informed consent form), same gender, and within age limits of ± 5 years to that of case; see section 5.2.1 for details of matching and Appendix A for details of administrative area by country). A flowchart of the control identification process is included in Appendix D.2.

The Investigator (or designated person) will document all potential controls in a Screening Log (Appendix C). This paper spreadsheet will allow documentation of date of identification, age and gender, current administrative area of residence, admission diagnosis (ICD-10) and the outcome of screening including reasons for non-participation (see section 6.4 for details of the Screening Log).

The Investigator (or designated person) will inform the identified control about all aspects of the study that are relevant to the patient's decision to participate and discuss his/her willingness to participate in the study. If the patient agrees and signs an informed consent form, the Investigator (or designated person) will enter control patient data (preliminary patient ID number, date of birth, gender, administrative area of residence (minimum 6 months prior to having signed the informed consent form) and date of informed consent) into the Patient Data Entry Screen of the DWS. The system then provides a control patient ID number which will be used to identify the control on all subsequent documentation. The control ID number will be reported to the CROs using the DWS. The DWS will also check the correctness of matching cases and controls (see section 7.1 for further details of the DWS).

If the DWS is unavailable or if a site does not have Internet access, a fax-based back-up system will be set up to report control recruitment and track the control ID number. In this scenario, faxed data completed by Investigators will be sent to and entered into the DWS by the dedicated CRO. The system will confirm patient ID numbers and check the database for correct matched patients. Notification will be confirmed to Investigators by fax.

The Investigator or interviewer will schedule an appointment for the face-to-face CAPI and the interviewer will update the interview status in the DWS (date interview scheduled/performed, interview status, date CD sent to PRADM). Patients who score less than 18 on the SMMSE cognitive test or do not complete the long questionnaire (see section 6.1), will have met one of the exclusion criteria (see section 5.2.5) and will therefore not be considered a control. Under these circumstances another control for the case will be sought.

If a principal site does not have access to a control within 2 months, a control will be recruited from another hospital or clinic as described in section 5.3.2.1 below.

5.3.2.1 Identification of Controls at another Hospital or Clinic (satellite sites)

If necessary, controls may be recruited from a hospital or clinic (satellite site) other than that where the cases (i.e. not from the principal sites) have been recruited. The Investigator (or designated person) at the satellite site will use the DWS with the data on the cases recruited from the principal site that require matched controls, to identify the matching controls. In addition to the inclusion criteria and exclusion criteria (stated in sections 5.2.4 and 5.2.5, respectively), the control must meet the matching criteria (see also section 5.2.1 for details of matching and Appendix A for details of administrative area by country).

The Investigator (or designated person) will document all potential controls in a Screening Log (Appendix C) as described for control patients at principal sites in section 5.3.2.

The Investigator (or designated person) at the satellite site will inform the control about all aspects of the study that are relevant to the patient's decision to participate and discuss his/her willingness to participate in the study. If the patient agrees and signs an informed consent form, the control patient ID number will be provided by the DWS as described for control patients at principal sites in section 5.3.2.

6 DATA SOURCES AND COLLECTION

6.1 Questionnaire

Life event history calendar (LEHC) questionnaires are an innovative technique which has proven useful in improving the quality and quantity of retrospective survey reports.[23,24] While LEHC questionnaires have not hitherto been used to a great extent in clinical and epidemiological studies, they represent an important advance for these fields. Methods using LEHC approaches are flexible enough to collect continuous measures of complex sequences of personal events and product usage because the LEHC questionnaire design more closely matches the structures of autobiographical memory recall than traditional questionnaires.[24] Recall of the precise timing of

specific life events (i.e. job titles or work duties) may present a cognitive challenge for some individuals. However, it has been shown that most individuals recall some important life events (i.e. year of marriage, birth of a child, start of a new job or year when someone moved to a new house). These more salient life events then act as cues to the recall of such ancillary issues as product usage (e.g. when I was pregnant with my first child I stopped drinking alcohol).

The C-TOR CAPI questionnaire is composed of several sections, namely introductory questions, the SMMSE cognitive test, LEHC questions, socioeconomic questions and a short version of the questionnaire (to be used for patients scoring less than 18 on the SMMSE). A copy of the paper-and-pencil version of the questionnaire is included in Appendix E.

The LEHC section of the questionnaire was developed to obtain data on a variety of life 'domains' (residence, life events, education, occupation, socioeconomic status, tobacco history, diet and alcohol use and medical history) and was designed to maximize the cues that are available in the memory of patients to aid them in recalling related or contemporaneous events in their life. The CAPI both collects data and acts as a memory aid. The CAPI's ability to display the information on the computer screen in an accessible form allows the patient to use cues from their own life, and remember events based on their interrelationships between domains (e.g. relates birth of child to stopping drinking alcohol). The interviewer will be trained to use different checking and cueing techniques to assist the patient in interrelating events as a method of identifying discrepancies with regard to the timing of events.

The CAPI will be the main data collection tool for obtaining information about the patient's smoking behavior, confounders and effect modifiers. Several studies have been conducted by university-affiliated experts to evaluate and validate the LEHC and the CAPI.[25] Areas that have been evaluated include: questionnaire design, questionnaire administration procedures, interviewer training and patient response to the questionnaire. The data gathering instrument has been reviewed and improved upon based on the results of the validation work, insuring that the current version of the C-TOR CAPI questionnaire is ready to be implemented in the field.

The validation studies have highlighted the need for interviewers to be selected based on their suitability to interact with patients, their ability to use the CAPI, as well as the need for interviewers to be extensively trained for the interviewing process through in-person training sessions using an interviewer training manual.[25] The results of the validation studies have been incorporated into the interviewer training procedures to optimize interviewer performance, in order to warrant that the highest possible quality of data is gathered while safeguarding the rights and well-being of the patient.[26] The interviewer training will also cover the ability to recognize patient discomfort and to terminate the interview early, if necessary, to minimize patient stress. Each interviewer will also require certification as to their being qualified to conduct the interviews.

The interviewing technique will be standardized throughout the study. In order to minimize bias between cases and controls, an attempt will be made to assign the same interviewer to both case and matched control interviews.[19] Furthermore, as an additional quality measure, an interview validation system will be implemented

throughout the study to assure consistency of data collection (i.e. consistency in the interviews carried out by each interviewer and consistency among different interviewers).

The interviewer validation system will require that all interviews where patient's permission is obtained should be audio recorded. The patient will be required to sign an informed consent form if they agree to the interview being recorded (Appendix F). If the patient refuses to allow the interview to be recorded, the recorder will be switched off before the interview begins. Trained monitors will listen to the audio recordings of more than 10% of all the interviews and evaluate the performance of the interviewer based on a predefined coding system.[26] It is planned that four of the first ten audio recorded interviews carried out by an individual interviewer will be monitored. A random selection of approximately 10% of all further audio recorded interviews will also be monitored. The interviewer will not be aware of which interview is likely to be monitored. A feedback system will be established to inform, re-train and subsequently intensely monitor those interviewers identified as not executing the interviews within the parameters established in the design and validation of the CAPI. This performance monitoring will also identify if, in any way, the interviewer is not respecting the rights and well-being of the patient (see section 10.11). All audio recordings will be destroyed after performance monitoring has been taken place (audio recordings which are not used for performance assessment will also be destroyed).

6.1.1 Questionnaire Administration

A trained interviewer from a CRO will administer the CAPI to cases and controls. The interviews will be performed by the interviewers in private after the patients have been informed about all aspects of the study and after they have given their written informed consent. The interview will normally take place within two months of written informed consent. However, given the medical and potential psychological condition of the patients, a patient can be declared unsuitable for interview at any given time by the Investigator (or designated person or interviewer).

Before starting the LEHC section of the questionnaire all patients will be asked to complete the SMMSE cognitive test as an assessment of their cognitive capability to respond reliably to the questionnaire.[16] Patients who score less than 18 points in the SMMSE will not be asked questions from the LEHC section of the questionnaire but will be asked to answer more general questions about their educational and socioeconomic status and their smoking history (Appendix E, Short Questionnaire). The short questionnaire was designed to minimize the potential for distress among patients who may not be suitable for the full interview and may become upset that the interview was discontinued because they "failed the test."

Patients who score less than 18 on the SMMSE cognitive test will have met one of the exclusion criteria. Cases scoring less than 18 on the SMMSE cognitive test will not be matched with a control and if a matched control scores less than 18 on the SMMSE cognitive test another control for the documented case will be sought.

The questionnaire will be administered to both cases and controls in the same manner.

The information gathered during the interviews will be entered directly into a laptop computer by the interviewer. Only certain information will be transmitted for data analysis; information related to cueing questions will be deleted as soon as the interview has been completed (see section 7 for further details of data transfer).

6.2 Medical Records

The Investigator (or designated person) is obligated to inform the patient (both cases and controls) that his/her medical records will be reviewed by an authorized representative of the CRO (study monitor), without violating the confidentiality of the patient. By signing the informed consent form, the patient agrees that his/her records may be consulted and/or copied by the CRO, Independent Ethics Committees (IEC), representatives of the Sponsor, or regulatory authority representatives in order to verify CRF data. Information about the diagnosis of lung cancer (cases) and primary diagnosis for hospital admission (controls) will be transcribed from the patient's medical records onto a CRF by the Investigator (or designated person) once written informed consent has been obtained, and prior to performing any study-related procedures. An example CRF is shown in Appendix G.

The CRFs are printed on 2-part, no-carbon-required paper. The Investigator (or designated person) is responsible for the accuracy of the transcribed data. The study monitor will review source records to assure the quality of the transcribed data.

The following data will be extracted for cases and controls:

- Primary diagnosis and manner determined (e.g. histological, cytological reports), medical chart confirmation for cases and diagnosis for hospital admission and diagnostic measures for controls
- Date of diagnosis

The monitor should have access to patient medical records and other C-TOR Study related records needed to verify the entries on the CRFs made by the Investigator (or designated person). The monitor will review the CRFs for completeness and accuracy, and instruct the Investigator (or designated person) to make any required corrections or additions. Direct access to patient medical records includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. If C-TOR Study documents need to be photocopied, the patients' name will be masked; patient initials will be visible, but the patient will be identified by the unique patient ID number only.

6.3 Laboratory/Pathology Data Collection

No laboratory assessment or pathology data will be collected in the C-TOR Study.

6.4 Screening Log

The Investigator (or designated person) will document all potential cases and controls in a Screening Log (Appendix C). This paper spreadsheet will allow documentation of date of identification, age and gender, current administrative area of residence, admission diagnosis (ICD-10) and outcome of screening. If the patient is not participating, the reason will be coded (*1 = selection criteria not met, 2 = not willing to participate in a study financially supported by a tobacco company, 3 = not willing*

to participate due to other reasons, 4 = not available (left hospital, died), 5 = unable to participate in the interview, 9 = other reasons, please specify). The screening data collected at the sites will not be included in the study database but will be transcribed to an electronic spreadsheet (see section 7.4).

7 DATA ENTRY AND DATA MANAGEMENT

A summary of collection, entry, and flow of all administrative data via the DWS, medical data and questionnaire data is included in Appendices H. Full details will be provided in a data management plan[26] which will be prepared before the C-TOR Study commences.

7.1 Dynamic Web-Based System (DWS)

During the C-TOR Study the DWS will be used for coordinating, collecting and reporting administrative data while assuring patient privacy. Data entry will utilize three entry screens and will allow entry of Investigator details, entry of patient administrative data and entry of interview status. The DWS will have a hierarchical access system with restricted data entry (write) access and/or read only access. Only Investigators, interviewers and monitors will have read/write access for their specific tasks and for their sites and patients. In addition, read access will be granted to the Sponsor, CRO Project Management and PRADM for all data. This will help ensure data security. Data will be transferred weekly to PRADM for uploading into the PRA standard clinical data management system.

On entry into the system, empty data entry screens will allow those with write access to enter the appropriate data for their task. Updates to patient status will be made, and for monitors and Investigators, the system will provide investigator and patient ID numbers.

Following data entry, hard copies may be printed by the Investigators for filing purposes and for cross-referencing/audits.

After logging into the DWS using a user name/ID code, the system will allow access to accurate and current study status information and will allow up-to-date report creation. The DWS is designed to permit data changes in such a way that the changes are documented in an audit trail.

A detailed plan of the web-based patient identification and reporting process will be prepared before the C-TOR Study commences. Details of the DWS can be found in the Manual of Operations and Procedures.[26]

7.2 Questionnaire Data

The interviewer will log into the DWS using the interviewer name/ID code and will select a case or control from the appropriate sites. The DWS allows interviewers to retrieve status reports (with status of cases/controls), provides support for scheduling interviews and records interview status.

The information collected by the interviewer during the interviews (see section 6.1.1) will be entered directly into a laptop computer. Encrypted data will be burnt onto a

CD and sent via courier to PRADM to be entered into the study database. One copy will be retained at the study site. One copy, which will also contain the audio recording (where this has been recorded with the consent of the patient), will be sent to the CRO for interviewer performance assessment purposes. The date the CDs are sent will also be recorded in the DWS.

7.3 Case Report Forms (CRFs)

Once the informed consent has been signed, the Investigators will complete the CRF. The completed CRFs will be collected during monitoring visits and sent to PRADM by the study monitors. In addition, a copy will be retained at the investigational site. The receipt of the CRFs will be tracked by PRADM. After having been scanned, the CRFs will be placed in central files. Data items from the CRFs will be entered into the study database using double data entry with electronic verification.

7.4 Screening Log

The paper Screening Logs will be collected during monitoring visits, and copied and sent to PRADM by the study monitors. The original Screening Log will be retained in the site files. PRADM will transcribe data from the Screening Logs to an electronic spreadsheet which will be used for ongoing analysis of enrollment response rates for cases and controls. Enrollment response rate analyses will be calculated after 100, 500 and 1,500 patients have been enrolled and after enrollment has been completed.

7.5 Database

As described in Appendix H the 'clean' patient data are quality checked and included in the final PRADM database which will be exported periodically to the Biometrics Group at Axio Research Corporation according to agreed data transfer specifications. Logic checks will be performed by PRADM prior to data delivery to the Biometrics Group. The C-TOR Study Data Oversight Committee will be responsible for assessing the data once the study is underway. The focus of interim data review will be data quality and quantity, and to confirm study assumptions. The final datasets will be used for statistical analyses.

8 SAMPLE SIZE

The calculation of the C-TOR Study sample size is based on statistical and study-specific assumptions. The assumptions are as follows:

- relative risk of lung cancer for FF to ULT: 1.33 (or 25% reduction from FF to ULT; study hypothesis)
- significance level: 5%, two-sided
- relative risk of lung cancer of current smokers to non-smokers: 15
- prevalence of smoking in the controls: 35%
- proportion of ULT smokers among controls: 1.8%
- proportion FF smokers among the controls: 23 %

To make a direct comparison of ULT and FF smokers (as specified in the primary objective), LT smokers and nonsmokers will be excluded from the analysis. It is estimated that this will exclude approx. 75% of controls and approx. 32% of cases.

Thus, the planned sample of 13,000 cases and 13,000 controls will provide approx 8,800 cases and approx 3,200 controls for this analysis. Based on market data, this sample is expected to include 1.8 % ULT smokers and 23% FF smokers in the control group. Meta-analysis of human tar exposure studies has pointed to a belief that the difference in odds of smoking ULT cigarettes between cases and controls will be in the order of 40%. Based on this assumption, a control group size of 13,000 patients and an equal number of cases will be required to produce a study of at least 90% power and 5% significance level. If the difference in the odds of smoking ULT cigarettes between cases and controls will be 33%, the power of this study would be 80% at the 5% significance level. If the difference is 25%, the planned sample will have a 55% power at the 5% significance level.

It is anticipated that a total of 26,000 patients (cases and matched controls) will be adequate to address the study objectives. The study-specific assumptions will be verified during the course of the study.

9 DATA ANALYSIS

9.1 Definition of Cigarette Use

Two sets of cigarette smoking definitions will be used in this study. The first is related to a classification of tar use for each individual patient and the second related to lifetime smoking status.

9.1.1 Lifetime Smoking Status

The lifetime smoking status is defined as follows[27]:

> *Ever cigarette smoker:* A patient with lifetime cigarette consumption of at least 100 cigarettes
>
> *Never cigarette smoker*: A patient with lifetime cigarette consumption of less than 100 cigarettes

The category of *ever cigarette smokers* is further subdivided into current and former cigarette smokers. Recognizing that many of the cases may have changed their smoking habits in the time leading up to the diagnosis/treatment of the lung cancer condition, the definition includes a 12-month period starting two years prior to signing the informed consent to allow for that potential change in smoking habits. The proposed definition for *current* and *former cigarette smokers* is as follows:

> *Former cigarette smoker*: A patient who has smoked at least 100 cigarettes in their lifetime, but has smoked less than 100 cigarettes in a 12 month period starting two years before signing the informed consent form.
>
> *Current cigarette smoker:* A patient who has smoked at least 100 cigarettes in their lifetime and has smoked at least 100 cigarettes in a 12 month period starting two years before signing the informed consent form.

9.1.2 Categories of Smokers

The proposed definitions of cigarette use are difficult to establish due to a lack of information regarding the average length of ULT use in patients as well as patient's

other smoking patterns. Additionally, because tar levels have changed continually over time, one can expect for the most part, that tar levels have decreased over time within brand.

The C-TOR Study is designed to provide an opportunity to review the smoking history of the study patients, and therefore, enable the development of a description of smoking patterns of study patients with regard to the prevalence of ULT, LT and FF cigarette smoking, the length of time the product of different tar content has been smoked, and the number of cigarettes of each type smoked.

For the purpose of testing the primary hypothesis, the following classifications are proposed:

Ultra-Low Tar (ULT) Smoker: A patient who

- is a current smoker of ULT (3 mg or less tar) cigarettes
- has smoked ULT cigarettes for a total of at least 8 calendar years
- is not a current smoker of pipes or cigars

Full Flavor (FF) Smoker: A patient who

- is a current smoker of FF (10 mg or more tar) cigarettes
- has smoked cigarettes for at least 8 calendar years
- is a never smoker of ULT (3 mg or less tar) or LT (greater than 3 mg and less than 10 mg tar) cigarettes
- is not a current smoker of pipes or cigars

Patients who have not completed the long version of the CAPI will not be considered for the primary analysis.

For the purposes of this study, current smokers of pipes or cigars are defined as follows:

Current pipe smoker: A patient who has smoked a pipe at least 100 times in their lifetime and has smoked a pipe at least 100 times in a 12 month period starting two years before the date of signing the informed consent form.

Current cigar smoker: A patient who has smoked at least 100 cigars in their lifetime and has smoked at least 100 cigars in a 12 month period starting two years before the date of signing the informed consent form.

Recognizing that many of the cases may have changed their smoking behavior in the time leading up to the diagnosis/treatment of the lung cancer condition, the definitions of *current cigar* and *current pipe smokers* includes a 12 month period starting two years prior to signing the informed consent form to allow for that potential change in smoking habits.

9.1.3 Tar Level

Due to the historic evolving nature of cigarettes, reduced yields products have gone by a variety of names including lights, ultra-lights, low tar (LT) and ultra-low tar (ULT). Non-reduced-tar products are normally referred to as full flavor (FF). These

names are not standardized and have not been coded at a national or international level. In fact, they have meant different things at different times. Tar content is measured by a standardized, machine-based process, in accordance with ISO or US Federal Trade Commission (FTC) standards, with a specified number of puffs of specified duration. These methodologies are essentially equivalent. Actual smoking practices vary among individuals, so this idealized machine-measured yield is not likely to correspond to the actual tar intake of the individual smoker.

Historically, FF filtered cigarettes yields have been as high as 22 mg of tar, as measured by this ISO or FTC methods which are essentially equivalent, and have typically been in the range of 15 to 17 mg, while a low tar product would have been one with a machine-measured yield of 13 mg. As of January 1, 2004, within the EU, the maximum tar yield has been reduced from to 12 mg to 10 mg.

For the purposes of this study the following definitions will apply which recognize the current status of the products on the market:

- Full Flavor (FF) – ISO machine-measured tar yield of 10 mg or more/cigarette
- Low Tar (LT) - ISO machine-measured tar yield of greater than 3 mg and less than 10 mg/cigarette
- Ultra-Low Tar (ULT) - ISO machine-measured tar yield of 3 mg or less/cigarette

These definitions will be applied to cigarettes smoked by study patients according to cigarette brand and year in relation to known tar level standards. Additional definitions may be applied within these tar level groupings if data allow.

9.2 Statistical Analysis

Stated as a null hypothesis, the primary objective of the study is to show that the risk of developing lung cancer associated with the use of ULT (3mg or less tar) cigarettes will not differ from that associated with the use of FF (10 mg or more tar) cigarettes by 25% or more.

Data analysis of the study will include primary analyses of the stated hypotheses as well as additional analyses to validate and examine the sensitivity of the hypotheses controlling for covariates, the heterogeneity of the results with respect to subgroups, and the amount and patterns of missing data in the study. All analyses will be two-sided inferences at 5% levels of significance.

An analysis of the initial patients will be used to validate the procedures, the overall sample size outlined in the protocol and the definitions of categories of smokers. The data from the first 100 patients will be used primarily to validate procedures such as data transfer, variable creation issues using multi-country data, and CAPI utilization. The data from the initial 500 up to 1,500 patients will be used to validate the smoking definitions set forth in section 9.1, review the overall sample size estimates needed for the study, examine patterns of missing data, and examine variability issues within and between investigational sites. These analyses will include an analysis of heterogeneity of the prevalence of smoking over countries; the use of the SMMSE as an inclusion/exclusion criteria; and the relationship between SMMSE, medical diagnosis and missing data in the C-TOR questionnaire. The C-TOR Data Oversight Committee will be responsible for assessing the interim results and providing recommendations

to the Sponsor regarding possible study modifications and amendments to the study protocol.

Specific details on the methodologies:

- The primary analysis will compare the odds ratios of lung cancer of ULT smokers and FF smokers in the case and control groups over all sites and countries.
- Efforts will be made to model the relationship between use of cigarettes of different nominal tar content, duration of use of different tar content cigarettes, amount of each type of product smoked and risk of lung cancer. Data from patients who have never smoked and who have ceased smoking will be included in the model. Additional analyses will be performed when sufficient data exist by country, study site, gender, age group, and other potential covariates.

Analyses will be carried out to assess potential heterogeneity between cases and controls with respect to non-smoking characteristics. In addition, unconditional logistic regression analysis will be used for adjustment and for identification of differential patterns and subgroups. The matching variables will be included in the model to assess residual confounding.

Descriptive analyses will be used to examine patient demographics. Such analyses are required to check the ability to combine data from individuals at different sites within countries and from different countries.

The impact of age, gender, and geographical distribution of the patients stratified both by smoking history in the dataset and in the datasets derived from the models which should show the relationship between product use, time of smoking each type of product and risk of development of lung cancer will be examined. These analyses will assist in understanding the relationship between the use of different nominal tar content cigarettes, time of use of different tar content cigarettes and risk for development of lung cancer.

Descriptive analyses will also be used to examine data transcribed from the Screening Logs and allow enrollment response rates for cases and controls.

Full details will be provided in the statistical analysis plan which will be prepared before the C-TOR Study commences.[26]

10 ADMINISTRATIVE CONSIDERATIONS

Details of the Sponsor, independent firms and academic institutions supporting the C-TOR Study can be found in Appendix B.

10.1 Informed Consent

The Investigator (or designated person), will inform the patient of all aspects of the study that are relevant to patient's decision to participate. The Investigator (or designated person) will explain to the patient that there *is no intended clinical benefit* to the patient during the participation in this epidemiological study. However, the results of this study will be of *public health interest.* The Investigator (or designated

person) will obtain written informed consent from each patient prior to initiation of study related procedures.

Patients will be informed about the C-TOR Study both verbally and in writing and will be given the opportunity to ask any questions. The Sponsor will provide a sample informed consent form which will then be tailored to address site-specific requirements. The final version must be authorized by the Sponsor, CROs, and the IECs, and it must contain all the elements in the sample form, in a language readily understood by the patient. Each patient's original consent form, personally signed and dated by the patient and by the person who conducted the informed consent discussion, will be retained by the Investigator at the study site. The Investigator (or designated person) will supply each enrolled patient with a copy of his/her signed informed consent form. The unique patient ID number will be assigned after the informed consent form has been signed and will be written on the form. The Investigator (or designated person) will record patient data, including date of signing informed consent, in the DWS (see also sections 5.3.1 and 5.3.2).

A sample (generic) copy of the informed consent form can be found in Appendix F.

10.2 Independent Ethics Committee (IEC) Approval

10.2.1 Ethical Considerations

The C-TOR Study will be conducted in accordance with good epidemiological practices and good clinical practices where applicable. In addition, the C-TOR Study will adhere to all local regulatory requirements. Appropriate electronic data handling practices and requirements for maintenance of patient privacy will be applied as governed by international codes and as required by national and local regulatory requirements.

10.2.2 Independent Ethics Committee Approval Process

Before enrollment starts, the Investigator will have written and dated approval from the responsible IEC for the study protocol; a written informed consent form and any consent form updates; patient recruitment procedures and any written information to be provided to patients. All amendments will be reviewed by the C-TOR Study Steering Committee. Those amendments identified as significant (e.g. not of a purely administrative nature) will be forwarded for consideration by the IEC.

The IEC approval must identify the protocol version as well as the documents reviewed (i.e. the informed consent and a printed copy of the questionnaire).

10.2.3 Regulatory Approval Process

The Sponsor (or CRO or any party authorized to act on behalf of the Sponsor) will obtain approval from the local regulatory authorities as appropriate.

10.3 Study Report

On completion of the C-TOR Study analyses, a study report will be prepared. A summary of the study report will be provided to each Investigator following completion of the report. Each site will receive a copy of the anonymized and aggregated data from the study in compliance with the relevant legislation.

10.4 Publication Policy

The C-TOR Publications and Presentations Committee (see Manual of Operations and Procedures[26] for details) will submit the results of the C-TOR Study for publication in a peer-reviewed journal irrespective of the outcome and regardless of the conclusions. Decisions regarding publications and presentations are the purview of the C-TOR Steering Committee. PMI, the financial backer of the C-TOR Study will not be involved in the preparation of the manuscripts or in the decision to submit publications. PMI will be given a copy of manuscripts submitted for publication. All publications will acknowledge the financial support of PMI.

The C-TOR Publications and Presentations Committee will assess additional opportunities for publication and presentations of data from the C-TOR Study. The committee will be charged with the task of guiding the Sponsor, C-TOR Study Steering Committee and Investigators through the decisions that will need to be made regarding additional C-TOR publications.

Specific site details and names of Investigators will only be included in publications upon agreement of the site Investigator.

10.5 Contractual and Financial Details

The Investigator (or designated person) and the CRO will sign a study agreement prior to start of the study at their site, outlining the CRO's, the Sponsor's and Investigator's overall responsibilities in relation to the study. Financial remuneration will cover the cost per included patient, based on the calculated costs of performing the study assessments in accordance with the protocol, and terms of payment will be described in the contract. Investigators will be compensated according to specified terms described in the contract. Reimbursement will not represent a significant financial interest for the Investigators.

10.6 Insurance, Indemnity and Compensation

The Sponsor will provide insurance for all patients against accidents at the study site caused by participating in the C-TOR Study, within the limits of the insurance provided by **Miller Insurance Services (UK) Limited**, Insurance House, 38 Croydon Road, Beckenham BR3 4BJ (registered in England: no. 3076036, registered office: Dawson House, 5 Jewry Street, London EC3N 2PJ, UK) according to the policy number **PWEI00105.**
In addition, the Sponsor will provide insurance for patients against accidents incurred while traveling to/from the study site to take part in the interview, within the limits of the insurance provided by **Miller Insurance Services (UK) Limited**, Insurance House, 38 Croydon Road, Beckenham BR3 4BJ (registered in England: no. 3076036, registered office: Dawson House, 5 Jewry Street, London EC3N 2PJ, UK) according to the policy number **IAH 0001168**. (For further details see informed consent form in Appendix F.)

10.7 Protocol Amendments

The study will follow the protocol strictly. If any changes become necessary, they must be agreed upon by the Investigators and the Sponsor and must be laid down in

an amendment to the protocol. The Sponsor and the Investigators must sign any amendments of the protocol. All amendments will be reviewed by the C-TOR Study Steering Committee. Those amendments identified as significant (e.g., not of a purely administrative nature) will be forwarded for consideration by the IEC.

10.8 Retention and Archiving of Records

10.8.1 Study Records

In compliance with good epidemiological and clinical practices where applicable, medical records/medical notes and associated items should be clearly marked and permit easy identification of participation by an individual in the C-TOR Study.

All clinical data relevant to each patient in the study will be recorded on CRFs designed and provided by the CRO. The Investigator (or designated person) will record all information requested on the CRFs or indicate why such information is not available. CRFs must be completed in ink in a timely manner and on an ongoing basis to allow regular review by the monitor. No changes are allowed unless initialed and dated by the Investigator (or designated person). Each CRF must be reviewed by the Investigator for accuracy and completeness, and the Investigator must sign each patient's CRF on the last page indicating his agreement with its contents and his certification of its accuracy. The monitor assigned by the Sponsor will review CRFs periodically and may bring to the site's attention the need for completion or reconciliation of data items. One complete set of CRFs will be provided to the CRO and one set retained at the site.

Following data entry into the DWS, hard copies may be printed by the Investigators for filing in site files and for cross-referencing/audits.

10.8.2 Record Retention

The Investigators of the principal and satellite sites must arrange for retention of C-TOR Study records in strict confidence of the patients' ID numbers, names and addresses for at least 10 years after the completion of the study.[30] Patients' files and other pertinent documentation (i.e. study protocol, signed informed consent forms, correspondence, and other documents pertaining to the conduct of the study) must be kept for the maximum period permitted by the hospital or private office in accordance with the local requirements, but not less than 10 years. No study documentation may be destroyed without written consent from the Sponsor.

If the Investigator relocates or retires, or otherwise withdraws his/her responsibility for record retention, the Sponsor must be notified (preferably in writing) so that adequate provisions can be made with regard to the study documents.

The Sponsor/CRO will retain all records relating to this study for a minimum of 10 years. Retention time must be sufficient to cover all potential publications of the data.

10.9 Confidentiality

The medical data obtained by the study represent personal information for each individual patient. It is therefore essential that the Investigator and site staff ensure

that this information is treated with sufficient care to assure the full confidentiality of each patient's information. Representatives of the Sponsor may review patient information periodically, and all personnel involved in such reviews will take precautions to maintain patient confidentiality. If C-TOR Study documents are to be collected by the Sponsor, the patients' name will be masked; patient initials will be visible but the patient will be identified by the unique patient ID number only.

If the Investigator later publishes any material concerning the results of this study, precautions will be taken to ensure that individual confidentiality is protected and that the patient's identity is kept confidential.

10.10 Quality Assurance and Regulatory Inspections

Quality assurance is defined as all those planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded), and reported to assure that the conclusions reached in the study are consistent with the findings. The Sponsor is required to put in place a quality assurance plan. Full details will be provided in the quality assurance plan which will be prepared by the Sponsor before the C-TOR Study commences.[26]

The Sponsor is responsible for securing agreement from all involved parties to assure direct access to all study related sites, source data, documents and reports for the purpose of auditing and monitoring by the Sponsor and inspection by domestic and foreign regulatory authorities.

The Investigator (or designated person) agrees to co-operate with the auditor during his/her visit and will be available to supply the auditor with all source data, document reports or other data necessary to conduct the audit.

In the event of the site being notified of a regulatory inspection, the Sponsor requests the Investigator (or designated person) to notify the Sponsor representative as soon as possible, to assist with preparations for the inspection.

10.11 Site Monitoring

The Investigator (or designated person) is responsible for the validity of all data entered to the CRF, DWS and Screening Log and the selection and qualification of the patients for participation in the study. The Sponsor has associated responsibilities with regard to monitoring. The purpose of site monitoring, which will be carried out by the CROs, is to verify that CRF study data are accurate (complete and verifiable to source data), that the patients are selected in compliance with the protocol. It is also the role of the monitor to insure that the rights of the patient in regards to privacy and data protection are protected and all other regulatory requirements are being adhered to.

A further element of site monitoring is the audio recording of interviews (see section 6.1). As indicated, the monitoring of the audio recordings for interviewer performance assessment will insure that the rights of the patient are being respected. All audio recordings will be destroyed after performance monitoring has been taken place (audio recordings which are not used for performance monitoring assessment will also be destroyed).

During monitoring visits, the monitor will:

- Check the progress of the study
- Verify the eligibility of subjects
- Ensure that all Informed consent forms have been signed
- Review study data collected
- Conduct source document verification and query any inconsistent entries into the CRF
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of patients are being protected
- The study is conducted in accordance with the approved protocol (and any amendments) and all applicable regulatory requirements
- Review and update regulatory binder

The site monitor will perform 100% source data verification with source records and will examine the record forms and other records for completeness and accuracy. The Investigator (or designated person) must allow Sponsor-authorized personnel direct access to medical charts and associated files for all study patients for the purpose of verifying entries made in the CRF. Investigators and site staff should make time available for monitoring visits and assist monitors in obtaining complete and accurate records of the study.

Documents that are to be collected for the Sponsor, should show only patient initials and be annotated with the unique patient ID number as identification. The name must be permanently blacked out by site personnel.

Monitors will visit the site to perform a Pre-Study Visit (section 4.2) in accordance with applicable regulations and study-specific Standard Operating Procedures (SOPs).[26] Qualified sites will receive a Site Initiation Visit prior to patient enrollment to allow protocol review and site staff training. A final Monitoring Visit will be made after termination of the study to finalize records and conclude the administrative portion of the study. In addition, monitors will conduct a Site Closure Visit to ensure all outstanding study data is returned to the CROs, resolve all pending data queries and review the site study records for completeness.

If the study is prematurely discontinued, all study data must be returned to the CROs and/or the Sponsor. In addition, arrangements will be made for the return of any electronic apparatus (such as computers or software) in accordance with the applicable procedures for the study.

10.12 Patient Withdrawal and Study Discontinuation

A patient has the right to withdraw consent or discontinue his/her participation in the study at any time without prejudice to his/her treatment. In addition, the Sponsor or CROs reserve the right to discontinue the patient from the study for any reason. The

Investigator also has the right to discontinue the patient from the study at his/her site for any reason.

In addition, the Sponsor reserves the right to suspend the study or discontinue it prematurely either at a single site or at all sites at any time for reasons including but not limited to: ethical issues; severe non-compliance with applicable regulatory requirements. If the Sponsor or CROs determine such action is needed, the Sponsor or CROs will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor or CROs will provide advance notification to the Investigator of the impending action prior to it taking effect.

The Sponsor and/or CROs will promptly inform all other Investigators and/or institutions conducting the study, as well as the relevant regulatory authorities, if the study is suspended or terminated and will provide the reasons for the action. If required by the applicable regulations, the Investigator must inform the IEC promptly and provide the reason for the suspension or termination.

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12 APPENDICES

APPENDIX A:
Country Administrative Areas for Matching[1]

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
ÖSTERREICH / AUSTRIA	**Bundesländer**	**Grupen von Politischen Bezirken**
AT11	**Burgenland**	
		Mittelburgenland
		Nordburgenland
		Südburgenland
AT12	**Niederösterreich**	
		Mostviertel-Eisenwurzen
		Niederösterreich-Süd
		Sankt Pölten
		Waldviertel
		Weinviertel
		Wiener Umland/Nordteil
		Wiener Umland/Südteil
AT13	**Wien**	
		Wien
AT21	**Kärnten**	
		Klagenfurt-Villach
		Oberkärnten
		Unterkärnten
AT22	**Steiermark**	
		Graz
		Liezen
		Östliche Obersteiermark
		Oststeiermark
		West- und Südsteiermark
		Westliche Obersteiermark
AT31	**Oberösterreich**	
		Innviertel
		Linz-Wels
		Mühlviertel
		Steyr-Kirchdorf
		Traunviertel
AT32	**Salzburg**	
		Lungau
		Pinzgau-Pongau
		Salzburg und Umgebung

[1] The Nomenclature of Territorial Units for Statistics (NUTS) is a geocode standard for referencing the administrative division of countries for statistical purposes. NUTS was created by the European Office for Statistics (Eurostat) and approved by the European Commission[32] as a single hierarchical classification of spatial units used for statistical production across the European Union.

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
ÖSTERREICH / AUSTRIA	**Bundesländer**	**Grupen von Politischen Bezirken**
AT33	**Tirol**	
		Außerfern
		Innsbruck
		Osttirol
		Tiroler Oberland
		Tiroler Unterland
AT34	**Vorarlberg**	
		Bludenz-Bregenzer Wald
		Rheintal-Bodenseegebiet
ATZZ	**Extra-Regio**	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
BELGIQUE/BELGIË BELGIUM	**Provincies/Provinces**	**Arrondissementen/ Arrondissements**
BE10	**Région de Bruxelles-Capitale / Brussels Hoofdstedelijk Gewest**	
		Arr. de Bruxelles-Capitale / Arr. van Brussel-Hoofdstad
BE21	**Prov. Antwerpen**	
		Arr. Antwerpen
		Arr. Mechelen
		Arr. Turnhout
BE22	**Prov. Limburg (B)**	
		Arr. Hasselt
		Arr. Maaseik
		Arr. Tongeren
BE23	**Prov. Oost-Vlaanderen**	
		Arr. Aalst
		Arr. Dendermonde
		Arr. Eeklo
		Arr. Gent
		Arr. Oudenaarde
		Arr. Sint-Niklaas
BE24	**Prov. Vlaams-Brabant**	
		Arr. Halle-Vilvoorde
		Arr. Leuven
BE25	**Prov. West-Vlaanderen**	
		Arr. Brugge
		Arr. Diksmuide
		Arr. Ieper
		Arr. Kortrijk
		Arr. Oostende
		Arr. Roeselare
		Arr. Tielt
		Arr. Veurne
BE31	**Prov. Brabant Wallon**	
		Arr. Nivelles

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
BELGIQUE/BELGIË BELGIUM	**Provincies/Provinces**	**Arrondissementen/ Arrondissements**
BE32	**Prov. Hainaut**	
		Arr. Ath
		Arr. Charleroi
		Arr. Mons
		Arr. Mouscron
		Arr. Soignies
		Arr. Thuin
		Arr. Tournai
BE33	**Prov. Liège**	
		Arr. Huy
		Arr. Liège
		Arr. Verviers
		Arr. Waremme
BE34	**Prov. Luxembourg (B)**	
		Arr. Arlon
		Arr. Bastogne
		Arr. Marche-en-Famenne
		Arr. Neufchâteau
		Arr. Virton
BE35	**Prov. Namur**	
		Arr. Dinant
		Arr. Namur
		Arr. Philippeville
BEZZ	**Extra-Regio**	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DE11	**Stuttgart**	
		Stuttgart, Stadtkreis
		Böblingen
		Esslingen
		Göppingen
		Ludwigsburg
		Rems-Murr-Kreis
		Heilbronn, Stadtkreis
		Heilbronn, Landkreis
		Hohenlohekreis
		Schwäbisch Hall
		Main-Tauber-Kreis
		Heidenheim
		Ostalbkreis
DE12	**Karlsruhe**	
		Baden-Baden, Stadtkreis
		Karlsruhe, Stadtkreis
		Karlsruhe, Landkreis
		Rastatt
		Heidelberg, Stadtkreis
		Mannheim, Stadtkreis
		Neckar-Odenwald-Kreis
		Rhein-Neckar-Kreis
		Pforzheim, Stadtkreis
		Calw
		Enzkreis
		Freudenstadt
DE13	**Freiburg**	
		Freiburg im Breisgau, Stadtkreis
		Breisgau-Hochschwarzwald
		Emmendingen
		Ortenaukreis
		Rottweil
		Schwarzwald-Baar-Kreis
		Tuttlingen
		Konstanz
		Lörrach
		Waldshut
DE14	**Tübingen**	
		Reutlingen
		Tübingen, Landkreis
		Zollernalbkreis
		Ulm, Stadtkreis
		Alb-Donau-Kreis
		Biberach
		Bodenseekreis

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DE14 (continued)	**Tübingen**	
		Ravensburg
		Sigmaringen
DE21	**Oberbayern**	
		Ingolstadt, Kreisfreie Stadt
		München, Kreisfreie Stadt
		Rosenheim, Kreisfreie Stadt
		Altötting
		Berchtesgadener Land
		Bad Tölz-Wolfratshausen
		Dachau
		Ebersberg
		Eichstätt
		Erding
		Freising
		Fürstenfeldbruck
		Garmisch-Partenkirchen
		Landsberg a. Lech
		Miesbach
		Mühldorf a. Inn
		München, Landkreis
		Neuburg-Schrobenhausen
		Pfaffenhofen a. d. Ilm
		Rosenheim, Landkreis
		Starnberg
		Traunstein
		Weilheim-Schongau
DE22	**Niederbayern**	
		Landshut, Kreisfreie Stadt
		Passau, Kreisfreie Stadt
		Straubing, Kreisfreie Stadt
		Deggendorf
		Freyung-Grafenau
		Kelheim
		Landshut, Landkreis
		Passau, Landkreis
		Regen
		Rottal-Inn
		Straubing-Bogen
		Dingolfing-Landau
DE23	**Oberpfalz**	
		Amberg, Kreisfreie Stadt
		Regensburg, Kreisfreie Stadt
		Weiden i. d. OPf.,Kreisfreie Stadt
		Amberg-Sulzbach
		Cham
		Neumarkt i. d. OPf.

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DE23 (continued)	**Oberpfalz**	
		Neustadt a. d. Waldnaab
		Regensburg, Landkreis
		Schwandorf
		Tirschenreuth
DE24	**Oberfranken**	
		Bamberg, Kreisfreie Stadt
		Bayreuth, Kreisfreie Stadt
		Coburg, Kreisfreie Stadt
		Hof, Kreisfreie Stadt
		Bamberg, Landkreis
		Bayreuth, Landkreis
		Coburg, Landkreis
		Forchheim
		Hof, Landkreis
		Kronach
		Kulmbach
		Lichtenfels
		Wunsiedel i. Fichtelgebirge
DE25	**Mittelfranken**	
		Ansbach, Kreisfreie Stadt
		Erlangen, Kreisfreie Stadt
		Fürth, Kreisfreie Stadt
		Nürnberg, Kreisfreie Stadt
		Schwabach, Kreisfreie Stadt
		Ansbach, Landkreis
		Erlangen-Höchstadt
		Fürth, Landkreis
		Nürnberger Land
		Neustadt a. d. Aisch-Bad Windsheim
		Roth
		Weißenburg-Gunzenhausen
DE26	**Unterfranken**	
		Aschaffenburg, Kreisfreie Stadt
		Schweinfurt, Kreisfreie Stadt
		Würzburg, Kreisfreie Stadt
		Aschaffenburg, Landkreis
		Bad Kissingen
		Rhön-Grabfeld
		Haßberge
		Kitzingen
		Miltenberg
		Main-Spessart
		Schweinfurt, Landkreis
		Würzburg, Landkreis

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DE27	**Schwaben**	
		Augsburg, Kreisfreie Stadt
		Kaufbeuren, Kreisfreie Stadt
		Kempten (Allgäu), Kreisfreie Stadt
		Memmingen, Kreisfreie Stadt
		Aichach-Friedberg
		Augsburg, Landkreis
		Dillingen a.d. Donau
		Günzburg
		Neu-Ulm
		Lindau (Bodensee)
		Ostallgäu
		Unterallgäu
		Donau-Ries
		Oberallgäu
DE30	**Berlin**	
		Berlin
DE41	**Brandenburg - Nordost**	
		Frankfurt (Oder), Kreisfreie Stadt
		Barnim
		Märkisch-Oderland
		Oberhavel
		Oder-Spree
		Ostprignitz-Ruppin
		Prignitz
		Uckermark
DE42	**Brandenburg - Südwest**	
		Brandenburg an der Havel, Kreisfreie Stadt
		Cottbus, Kreisfreie Stadt
		Potsdam, Kreisfreie Stadt
		Dahme-Spreewald
		Elbe-Elster
		Havelland
		Oberspreewald-Lausitz
		Potsdam-Mittelmark
		Spree-Neiße
		Teltow-Fläming
DE50	**Bremen**	
		Bremen, Kreisfreie Stadt
		Bremerhaven, Kreisfreie Stadt
DE60	**Hamburg**	
		Hamburg

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DE71	**Darmstadt**	
		Darmstadt, Kreisfreie Stadt
		Frankfurt am Main, Kreisfreie Stadt
		Offenbach am Main, Kreisfreie Stadt
		Wiesbaden, Kreisfreie Stadt
		Bergstraße
		Darmstadt-Dieburg
		Groß-Gerau
		Hochtaunuskreis
		Main-Kinzig-Kreis
		Main-Taunus-Kreis
		Odenwaldkreis
		Offenbach, Landkreis
		Rheingau-Taunus-Kreis
		Wetteraukreis
DE72	**Gießen**	
		Gießen, Landkreis
		Lahn-Dill-Kreis
		Limburg-Weilburg
		Marburg-Biedenkopf
		Vogelsbergkreis
DE73	**Kassel**	
		Kassel, Kreisfreie Stadt
		Fulda
		Hersfeld-Rotenburg
		Kassel, Landkreis
		Schwalm-Eder-Kreis
		Waldeck-Frankenberg
		Werra-Meißner-Kreis
DE80	**Mecklenburg-Vorpommern**	
		Greifswald, Kreisfreie Stadt
		Neubrandenburg, Kreisfreie Stadt
		Rostock, Kreisfreie Stadt
		Schwerin, Kreisfreie Stadt
		Stralsund, Kreisfreie Stadt
		Wismar, Kreisfreie Stadt
		Bad Doberan
		Demmin
		Güstrow
		Ludwigslust
		Mecklenburg-Strelitz
		Müritz
		Nordvorpommern
		Nordwestmecklenburg

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DE80 (continued)	**Mecklenburg-Vorpommern**	
		Ostvorpommern
		Parchim
		Rügen
		Uecker-Randow
DE91	**Braunschweig**	
		Braunschweig, Kreisfreie Stadt
		Salzgitter, Kreisfreie Stadt
		Wolfsburg, Kreisfreie Stadt
		Gifhorn
		Göttingen
		Goslar
		Helmstedt
		Northeim
		Osterode am Harz
		Peine
		Wolfenbüttel
DE92	**Hannover**	
		Diepholz
		Hameln-Pyrmont
		Hildesheim
		Holzminden
		Nienburg (Weser)
		Schaumburg
		Region Hannover
DE93	**Lüneburg**	
		Celle
		Cuxhaven
		Harburg
		Lüchow-Dannenberg
		Lüneburg, Landkreis
		Osterholz
		Rotenburg (Wümme)
		Soltau-Fallingbostel
		Stade
		Uelzen
		Verden
DE94	**Weser-Ems**	
		Delmenhorst, Kreisfreie Stadt
		Emden, Kreisfreie Stadt
		Oldenburg (Oldenburg), Kreisfreie Stadt
		Osnabrück, Kreisfreie Stadt
		Wilhelmshaven, Kreisfreie Stadt
		Ammerland
		Aurich

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DE94 (continued)	**Weser-Ems**	
		Cloppenburg
		Emsland
		Friesland
		Grafschaft Bentheim
		Leer
		Oldenburg, Landkreis
		Osnabrück, Landkreis
		Vechta
		Wesermarsch
		Wittmund
DEA1	**Düsseldorf**	
		Düsseldorf, Kreisfreie Stadt
		Duisburg, Kreisfreie Stadt
		Essen, Kreisfreie Stadt
		Krefeld, Kreisfreie Stadt
		Mönchengladbach, Kreisfreie Stadt
		Mülheim an der Ruhr,Kreisfreie Stadt
		Oberhausen, Kreisfreie Stadt
		Remscheid, Kreisfreie Stadt
		Solingen, Kreisfreie Stadt
		Wuppertal, Kreisfreie Stadt
		Kleve
		Mettmann
		Neuss
		Viersen
		Wesel
DEA2	**Köln**	
		Aachen, Kreisfreie Stadt
		Bonn, Kreisfreie Stadt
		Köln, Kreisfreie Stadt
		Leverkusen, Kreisfreie Stadt
		Aachen, Kreis
		Düren
		Erftkreis
		Euskirchen
		Heinsberg
		Oberbergischer Kreis
		Rheinisch-Bergischer Kreis
		Rhein-Sieg-Kreis
DEA3	**Münster**	
		Bottrop, Kreisfreie Stadt
		Gelsenkirchen, Kreisfreie Stadt
		Münster, Kreisfreie Stadt
		Borken
DEA3 (continued)	**Münster**	

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
		Coesfeld
		Recklinghausen
		Steinfurt
		Warendorf
DEA4	**Detmold**	
		Bielefeld, Kreisfreie Stadt
		Gütersloh
		Herford
		Höxter
		Lippe
		Minden-Lübbecke
		Paderborn
DEA5	**Arnsberg**	
		Bochum, Kreisfreie Stadt
		Dortmund, Kreisfreie Stadt
		Hagen, Kreisfreie Stadt
		Hamm, Kreisfreie Stadt
		Herne, Kreisfreie Stadt
		Ennepe-Ruhr-Kreis
		Hochsauerlandkreis
		Märkischer Kreis
		Olpe
		Siegen-Wittgenstein
		Soest
		Unna
DEB1	**Koblenz**	
		Koblenz, Kreisfreie Stadt
		Ahrweiler
		Altenkirchen (Westerwald)
		Bad Kreuznach
		Birkenfeld
		Cochem-Zell
		Mayen-Koblenz
		Neuwied
		Rhein-Hunsrück-Kreis
		Rhein-Lahn-Kreis
		Westerwaldkreis
DEB2	**Trier**	
		Trier, Kreisfreie Stadt
		Bernkastel-Wittlich
		Bitburg-Prüm
		Daun
		Trier-Saarburg

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DEB3	**Rheinhessen-Pfalz**	
		Frankenthal (Pfalz), Kreisfreie Stadt
		Kaiserslautern, Kreisfreie Stadt
		Landau in der Pfalz, Kreisfreie Stadt
		Ludwigshafen am Rhein, Kreisfreie Stadt
		Mainz, Kreisfreie Stadt
		Neustadt an der Weinstraße, Kreisfreie Stadt
		Pirmasens, Kreisfreie Stadt
		Speyer, Kreisfreie Stadt
		Worms, Kreisfreie Stadt
		Zweibrücken, Kreisfreie Stadt
		Alzey-Worms
		Bad Dürkheim
		Donnersbergkreis
		Germersheim
		Kaiserslautern, Landkreis
		Kusel
		Südliche Weinstraße
		Ludwigshafen, Landkreis
		Mainz-Bingen
		Südwestpfalz
DEC0	**Saarland**	
		Stadtverband Saarbrücken
		Merzig-Wadern
		Neunkirchen
		Saarlouis
		Saarpfalz-Kreis
		St. Wendel
DED1	**Chemnitz**	
		Chemnitz, Kreisfreie Stadt
		Plauen, Kreisfreie Stadt
		Zwickau, Kreisfreie Stadt
		Annaberg
		Chemnitzer Land
		Freiberg
		Vogtlandkreis
		Mittlerer Erzgebirgskreis
		Mittweida
		Stollberg
		Aue-Schwarzenberg
		Zwickauer Land

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DED2	**Dresden**	
		Dresden, Kreisfreie Stadt
		Görlitz, Kreisfreie Stadt
		Hoyerswerda, Kreisfreie Stadt
		Bautzen
		Meißen
		Niederschlesischer Oberlausitzkreis
		Riesa-Großenhain
		Löbau-Zittau
		Sächsische Schweiz
		Weißeritzkreis
		Kamenz
DED3	**Leipzig**	
		Leipzig, Kreisfreie Stadt
		Delitzsch
		Döbeln
		Leipziger Land
		Muldentalkreis
		Torgau-Oschatz
DEE1	**Dessau**	
		Dessau, Kreisfreie Stadt
		Anhalt-Zerbst
		Bernburg
		Bitterfeld
		Köthen
		Wittenberg
DEE2	**Halle**	
		Halle (Saale), Kreisfreie Stadt
		Burgenlandkreis
		Mansfelder Land
		Merseburg-Querfurt
		Saalkreis
		Sangerhausen
		Weißenfels
DEE3	**Magdeburg**	
		Magdeburg, Kreisfreie Stadt
		Aschersleben-Staßfurt
		Bördekreis
		Halberstadt
		Jerichower Land
		Ohrekreis
		Stendal
		Quedlinburg
		Schönebeck
		Wernigerode
		Altmarkkreis Salzwedel

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
DEUTSCHLAND/ GERMANY	**Regierungsbezirke**	**Kreise/kreisfreie Städte**
DEF0	**Schleswig-Holstein**	
		Flensburg, Kreisfreie Stadt
		Kiel, Kreisfreie Stadt
		Lübeck, Kreisfreie Stadt
		Neumünster, Kreisfreie Stadt
		Dithmarschen
		Herzogtum Lauenburg
		Nordfriesland
		Ostholstein
		Pinneberg
		Plön
		Rendsburg-Eckernförde
		Schleswig-Flensburg
		Segeberg
		Steinburg
		Stormarn
DEG0	**Thüringen**	
		Erfurt, Kreisfreie Stadt
		Gera, Kreisfreie Stadt
		Jena, Kreisfreie Stadt
		Suhl, Kreisfreie Stadt
		Weimar, Kreisfreie Stadt
		Eichsfeld
		Nordhausen
		Unstrut-Hainich-Kreis
		Kyffhäuserkreis
		Schmalkalden-Meiningen
		Gotha
		Sömmerda
		Hildburghausen
		Ilm-Kreis
		Weimarer Land
		Sonneberg
		Saalfeld-Rudolstadt
		Saale-Holzland-Kreis
		Saale-Orla-Kreis
		Greiz
		Altenburger Land
		Eisenach, Kreisfreie Stadt
		Wartburgkreis
DEZZ	**Extra-Regio**	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
SUOMI / FINLAND	**Suuralueet / Storområden**	**Maakunnat/Landskapen**
FI13	**Itä-Suomi**	
		Etelä-Savo
		Pohjois-Savo
		Pohjois-Karjala
		Kainuu
FI18	**Etelä-Suomi**	
		Uusimaa
		Itä-Uusimaa
		Varsinais-Suomi
		Kanta-Häme
		Päijät-Häme
		Kymenlaakso
		Etelä-Karjala
FI19	**Länsi-Suomi**	
		Satakunta
		Pirkanmaa
		Keski-Suomi
		Etelä-Pohjanmaa
		Pohjanmaa
FI1A	**Pohjois-Suomi**	
		Keski-Pohjanmaa
		Pohjois-Pohjanmaa
		Lappi
FI20	**Åland**	
		Åland
FIZZ	**Extra-Regio**	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
FRANCE	**Régions + DOM**	**Départments + DOM**
FR10	**Île de France**	
		Paris
		Seine-et-Marne
		Yvelines
		Essonne
		Hauts-de-Seine
		Seine-Saint-Denis
		Val-de-Marne
		Val-d'Oise
FR21	**Champagne-Ardenne**	
		Ardennes
		Aube
		Marne
		Haute-Marne
FR22	**Picardie**	
		Aisne
		Oise
		Somme
FR23	**Haute-Normandie**	
		Eure
		Seine-Maritime
FR24	**Centre**	
		Cher
		Eure-et-Loir
		Indre
		Indre-et-Loire
		Loir-et-Cher
		Loiret
FR25	**Basse-Normandie**	
		Calvados
		Manche
		Orne
FR26	**Bourgogne**	
		Côte-d'Or
		Nièvre
		Saône-et-Loire
		Yonne
FR30	**Nord - Pas-de-Calais**	
		Nord
		Pas-de-Calais
FR41	**Lorraine**	
		Meurthe-et-Moselle
		Meuse
		Moselle
		Vosges
FR42	**Alsace**	

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
FRANCE	**Régions + DOM**	**Départments + DOM**
		Bas-Rhin
		Haut-Rhin
FR43	**Franche-Comté**	
		Doubs
		Jura
		Haute-Saône
		Territoire de Belfort
FR51	**Pays de la Loire**	
		Loire-Atlantique
		Maine-et-Loire
		Mayenne
		Sarthe
		Vendée
FR52	**Bretagne**	
		Côtes-d'Armor
		Finistère
		Ille-et-Vilaine
		Morbihan
FR53	**Poitou-Charentes**	
		Charente
		Charente-Maritime
		Deux-Sèvres
		Vienne
FR61	**Aquitaine**	
		Dordogne
		Gironde
		Landes
		Lot-et-Garonne
		Pyrénées-Atlantiques
FR62	**Midi-Pyrénées**	
		Ariège
		Aveyron
		Haute-Garonne
		Gers
		Lot
		Hautes-Pyrénées
		Tarn
		Tarn-et-Garonne
FR63	**Limousin**	
		Corrèze
		Creuse
		Haute-Vienne
FR71	**Rhône-Alpes**	
		Ain
		Ardèche
		Drôme
FR71 (continued)	**Rhône-Alpes**	

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
FRANCE	**Régions + DOM**	**Départments + DOM**
		Isère
		Loire
		Rhône
		Savoie
		Haute-Savoie
FR72	**Auvergne**	
		Allier
		Cantal
		Haute-Loire
		Puy-de-Dôme
FR81	**Languedoc-Roussillon**	
		Aude
		Gard
		Hérault
		Lozère
		Pyrénées-Orientales
FR82	**Provence-Alpes-Côte d'Azur**	
		Alpes-de-Haute-Provence
		Hautes-Alpes
		Alpes-Maritimes
		Bouches-du-Rhône
		Var
		Vaucluse
FR83	**Corse**	
		Corse-du-Sud
		Haute-Corse
FR91	**Guadeloupe**	
		Guadeloupe
FR92	**Martinique**	
		Martinique
FR93	**Guyane**	
		Guyane
FR94	**Réunion**	
		Réunion
FRZZ	**Extra-Regio**	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
ELLADA / GREECE	**Periferies**	**Nomoi**
GR11	**Anatoliki Makedonia, Thraki**	
		Evros
		Xanthi
		Rodopi
		Drama
		Kavala
GR12	**Kentriki Makedonia**	
		Imathia
		Thessaloniki
		Kilkis
		Pella
		Pieria
		Serres
		Chalkidiki
GR13	**Dytiki Makedonia**	
		Grevena
		Kastoria
		Kozani
		Florina
GR14	**Thessalia**	
		Karditsa
		Larisa
		Magnisia
		Trikala
GR21	**Ipeiros**	
		Arta
		Thesprotia
		Ioannina
		Preveza
GR22	**Ionia Nisia**	
		Zakynthos
		Kerkyra
		Kefallinia
		Lefkada
GR23	**Dytiki Ellada**	
		Aitoloakarnania
		Achaia
		Ileia
GR24	**Sterea Ellada**	
		Voiotia
		Evvoia
		Evrytania
		Fthiotida
		Fokida
GR25	**Peloponnisos**	

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
ELLADA / GREECE	**Periferies**	**Nomoi**
		Argolida
		Arkadia
		Korinthia
		Lakonia
		Messinia
GR30	**Attiki**	
		Attiki
GR41	**Voreio Aigaio**	
		Lesvos
		Samos
		Chios
GR42	**Notio Aigaio**	
		Dodekanisos
		Kyklades
GR43	**Kriti**	
		Irakleio
		Lasithi
		Rethymni
		Chania
GRZZ	**Extra-Regio**	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
MAGYARORSZAG / HUNGARY	**Statistical Regions**	**Counties**
HU10	**Kozep-Magyarorszag**	
		Budapest
		Pest
HU21	**Kozep-Dunantul**	
		Fejer
		Komarom-Esztergom
		Veszprem
HU22	**Nyugat-Dunantul**	
		Gyor-Moson-Sopron
		Vas
		Zala
HU23	**Del-Dunantul**	
		Baranya
		Somogy
		Tolna
HU31	**Eszak-Magyarorszag**	
		Borsod-Abauj-Zemplen
		Heves
		Nograd
HU32	**Eszak-Alfold**	
		Hajdu-Bihar
		Jasz-Nagykun-Szolnok
		Szabolcs-Szatmar-Bereg
HU33	**Del-Alfold**	
		Bacs-Kiskun
		Bekes
		Csongrad
HUZZ	**Extra-Regio**	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
ITALIA / ITALY	**Regioni**	**Provincie**
ITC1	**Piemonte**	
		Torino
		Vercelli
		Biella
		Verbano-Cusio-Ossola
		Novara
		Cuneo
		Asti
		Alessandria
ITC2	**Valle d'Aosta/Vallée d'Aoste**	
		Valle d'Aosta/Vallée d'Aoste
ITC3	**Liguria**	
		Imperia
		Savona
		Genova
		La Spezia
ITC4	**Lombardia**	
		Varese
		Como
		Lecco
		Sondrio
		Milano
		Bergamo
		Brescia
		Pavia
		Lodi
		Cremona
		Mantova
ITD1	**Provincia Autonoma Bolzano/Bozen**	
		Bolzano-Bozen
ITD2	**Provincia Autonoma Trento**	
		Trento
ITD3	**Veneto**	
		Verona
		Vicenza
		Belluno
		Treviso
		Venezia
		Padova
		Rovigo

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
ITALIA / ITALY	**Regioni**	**Provincie**
ITD4	**Friuli-Venezia Giulia**	
		Pordenone
		Udine
		Gorizia
		Trieste
ITD5	**Emilia-Romagna**	
		Piacenza
		Parma
		Reggio nell'Emilia
		Modena
		Bologna
		Ferrara
		Ravenna
		Forlì-Cesena
		Rimini
ITE1	**Toscana**	
		Massa-Carrara
		Lucca
		Pistoia
		Firenze
		Prato
		Livorno
		Pisa
		Arezzo
		Siena
		Grosseto
ITE2	**Umbria**	
		Perugia
		Terni
ITE3	**Marche**	
		Pesaro e Urbino
		Ancona
		Macerata
		Ascoli Piceno
ITE4	**Lazio**	
		Viterbo
		Rieti
		Roma
		Latina
		Frosinone
ITF1	**Abruzzo**	
		L'Aquila
		Teramo
		Pescara
		Chieti

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
ITALIA / ITALY	**Regioni**	**Provincie**
ITF2	**Molise**	
		Isernia
		Campobasso
ITF3	**Campania**	
		Caserta
		Benevento
		Napoli
		Avellino
		Salerno
ITF4	**Puglia**	
		Foggia
		Bari
		Taranto
		Brindisi
		Lecce
ITF5	**Basilicata**	
		Potenza
		Matera
ITF6	**Calabria**	
		Cosenza
		Crotone
		Catanzaro
		Vibo Valentia
		Reggio di Calabria
ITG1	**Sicilia**	
		Trapani
		Palermo
		Messina
		Agrigento
		Caltanissetta
		Enna
		Catania
		Ragusa
		Siracusa
ITG2	**Sardegna**	
		Sassari
		Nuoro
		Oristano
		Cagliari
ITZZ	**Extra-Regio**	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
SCHWEIZ / SUISSE / SVIZZERA SWITZERLAND	**Groupings of Cantons**	**Cantons**
CH01	**Région lémanique**	
		Vaud
		Valais
		Genève
CH02	**Espace Mittelland**	
		Bern
		Freiburg
		Solothurn
		Neuchâtel
		Jura
CH03	**Nordwestschweiz**	
		Basel-Stadt
		Basel-Landschaft
		Aargau
CH04	**Zürich**	
		Zürich
CH05	**Ostschweiz**	
		Glarus
		Schaffhausen
		Appenzell Ausserrhoden
		Appenzell Innerrhoden
		St. Gallen
		Graubünden
		Thurgau
CH06	**Zentralschweiz**	
		Luzern
		Uri
		Schwyz
		Obwalden
		Nidwalden
		Zug
CH07	**Ticino**	
		Ticino

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
SLOVENIJA/ SLOVENIA	**Country**	**Statisticne Regije**
SI00	**Slovenija**	
		Pomurska
		Podravska
		Koroska
		Savinjska
		Zasavska
		Spodnjeposavska
		Gorenjska
		Notranjsko-kraska
		Goriska
		Obalno-kraska
		Jugovzhodna Slovenija
		Osrednjeslovenska
	Extra-Regio	
		Extra-Regio

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
UNITED KINGDOM	**Group of Counties**	**Counties/Local Authority Regions**
UKC1	**Tees Valley and Durham**	
		Hartlepool and Stockton-on-Tees
		South Teesside
		Darlington
		Durham CC
UKC2	**Northumberland and Tyne and Wear**	
		Northumberland
		Tyneside
		Sunderland
UKD1	**Cumbria**	
		West Cumbria
		East Cumbria
UKD2	**Cheshire**	
		Halton and Warrington
		Cheshire CC
UKD3	**Greater Manchester**	
		Greater Manchester South
		Greater Manchester North
UKD4	**Lancashire**	
		Blackburn with Darwen
		Blackpool
		Lancashire CC
UKD5	**Merseyside**	
		East Merseyside
		Liverpool
		Sefton
		Wirral
UKE1	**East Riding and North Lincolnshire**	
		Kingston upon Hull, City of
		East Riding of Yorkshire
		North and North East Lincolnshire
UKE2	**North Yorkshire**	
		York
		North Yorkshire CC
UKE3	**South Yorkshire**	
		Barnsley, Doncaster and Rotherham
		Sheffield

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
UNITED KINGDOM	**Group of Counties**	**Counties/Local Authority Regions**
UKE4	**West Yorkshire**	
		Bradford
		Leeds
		Calderdale, Kirklees and Wakefield
UKF1	**Derbyshire and Nottinghamshire**	
		Derby
		East Derbyshire
		South and West Derbyshire
		Nottingham
		North Nottinghamshire
		South Nottinghamshire
UKF2	**Leicestershire, Rutland and Northamptonshire**	
		Leicester
		Leicestershire CC and Rutland
		Northamptonshire
UKF3	**Lincolnshire**	
		Lincolnshire
UKG1	**Herefordshire, Worcestershire and Warwickshire**	
		Herefordshire, County of
		Worcestershire
		Warwickshire
UKG2	**Shropshire and Staffordshire**	
		Telford and Wrekin
		Shropshire CC
		Stoke-on-Trent
		Staffordshire CC
UKG3	**West Midlands**	
		Birmingham
		Solihull
		Coventry
		Dudley and Sandwell
		Walsall and Wolverhampton
UKH1	**East Anglia**	
		Peterborough
		Cambridgeshire CC
		Norfolk
		Suffolk

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
UNITED KINGDOM	**Group of Counties**	**Counties/Local Authority Regions**
UKH2	**Bedfordshire and Hertfordshire**	
		Luton
		Bedfordshire CC
		Hertfordshire
UKH3	**Essex**	
		Southend-on-Sea
		Thurrock
		Essex CC
UKI1	**Inner London**	
		Inner London - West
		Inner London - East
UKI2	**Outer London**	
		Outer London - East and North East
		Outer London - South
		Outer London - West and North West
UKJ1	**Berkshire, Buckinghamshire and Oxfordshire**	
		Berkshire
		Milton Keynes
		Buckinghamshire CC
		Oxfordshire
UKJ2	**Surrey, East and West Sussex**	
		Brighton and Hove
		East Sussex CC
		Surrey
		West Sussex
UKJ3	**Hampshire and Isle of Wight**	
		Portsmouth
		Southampton
		Hampshire CC
		Isle of Wight
UKJ4	**Kent**	
		Medway
		Kent CC

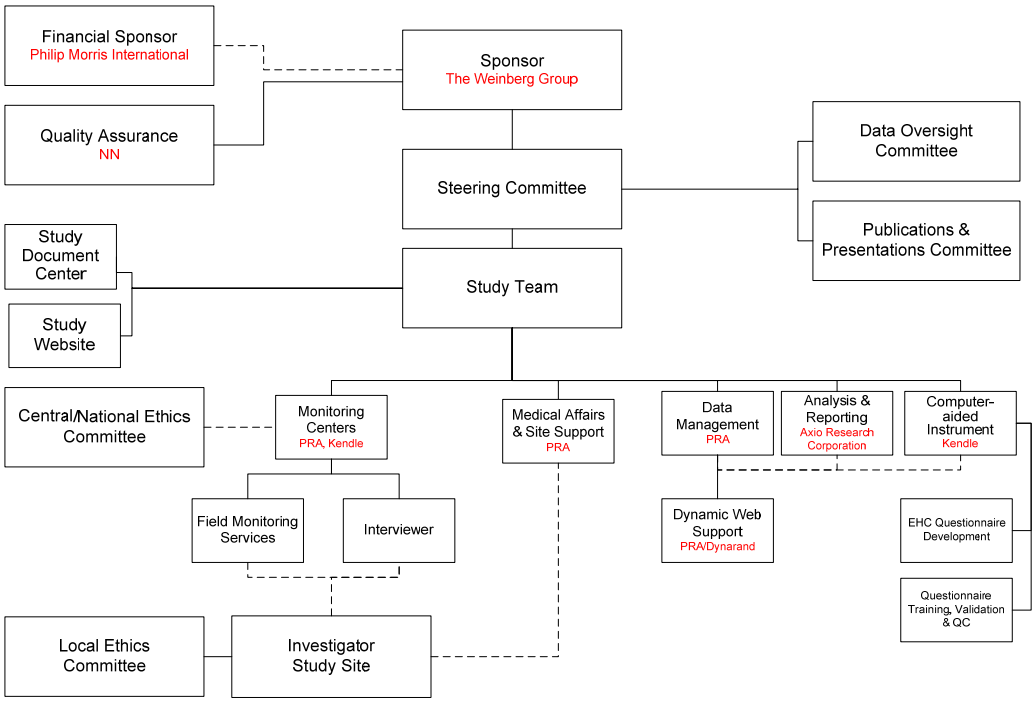
COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
UNITED KINGDOM	**Group of Counties**	**Counties/Local Authority Regions**
UKK1	**Gloucestershire, Wiltshire and North Somerset**	
		Bristol, City of
		North and North East Somerset, South Gloucestershire
		Gloucestershire
		Swindon
		Wiltshire CC
UKK2	**Dorset and Somerset**	
		Bournemouth and Poole
		Dorset CC
		Somerset
UKK3	**Cornwall and Isles of Scilly**	
		Cornwall and Isles of Scilly
UKK4	**Devon**	
		Plymouth
		Torbay
		Devon CC
UKL1	**West Wales and The Valleys**	
		Isle of Anglesey
		Gwynedd
		Conwy and Denbighshire
		South West Wales
		Central Valleys
		Gwent Valleys
		Bridgend and Neath Port Talbot
		Swansea
UKL2	**East Wales**	
		Monmouthshire and Newport
		Cardiff and Vale of Glamorgan
		Flintshire and Wrexham
		Powys
UKM1	**North Eastern Scotland**	
		Aberdeen City, Aberdeenshire and North East Moray

COUNTRY / CODE	REGIONS FOR MATCHING	SUBDIVISIONS FOR REFERENCE
UNITED KINGDOM	**Group of Counties**	**Counties/Local Authority Regions**
UKM2	**Eastern Scotland**	
		Angus and Dundee City
		Clackmannanshire and Fife
		East Lothian and Midlothian
		Scottish Borders, The
		Edinburgh, City of
		Falkirk
		Perth and Kinross and Stirling
		West Lothian
UKM3	**South Western Scotland**	
		East and West Dunbartonshire, Helensburgh and Lomond
		Dumfries and Galloway
		East Ayrshire and North Ayrshire Mainland
		Glasgow City
		Inverclyde, East Renfrewshire and Renfrewshire
		North Lanarkshire
		South Ayrshire
		South Lanarkshire
UKM4	**Highlands and Islands**	
		Caithness and Sutherland and Ross and Cromarty
		Inverness and Nairn and Moray, Badenoch and Strathspey
		Lochaber, Skye and Lochalsh and Argyll and the Islands
		Eilean Siar (Western Isles)
		Orkney Islands
		Shetland Islands
UKN0	**Northern Ireland**	
		Belfast
		Outer Belfast
		East of Northern Ireland
		North of Northern Ireland
		West and South of Northern Ireland
UKZZ	**Extra-Regio**	
		Extra-Regio

APPENDIX B:
Study Administrative Structure

Different groups are responsible for monitoring specific aspects of the C-TOR Study (see Figure below, C-TOR Study Organization). The final responsibility for the conduct of the study is with the Sponsor and the Investigators.

C-TOR Study Organization



Various groups comprised of independent firms and academic institutions are involved in the C-TOR Study. A brief outline of their roles and responsibilities is presented here. Details of the administrative structure and organization of the C-TOR Study are described in the Manual of Operations and Procedures.[26]

- **Steering Committee**

  Appointed by the Sponsor and comprised of experts not directly involved in the study and Sponsor personnel. While blinded, the Steering Committee acts as an independent body that takes responsibility for the scientific and ethical integrity of the C-TOR Study. Among others, the Steering Committee takes responsibility for the scientific validity of the study protocol, independent assessment of study quality and conduct as well as for the scientific quality of the final report. The Steering Committee is responsible for communication between the Data Oversight Committee and the Sponsor. An additional task of this committee is the approval of C-TOR Study documents (e.g. C-TOR Study protocol) and for any subsequent changes, the Steering Committee is responsible for assessing if IEC appraisal is required.

- **Data Oversight Committee**

  Composed of independent experts external to the C-TOR Study, this committee reviews unblinded study information during the conduct of the study. Based on its review the Data Oversight Committee provides the Steering Committee/Sponsor with recommendations regarding study modifications, continuation or termination.

- **Publications and Presentations Committee**

  This committee will submit the results of the C-TOR Study in a peer-reviewed journal and will assess additional opportunities for publications and presentations of data from the C-TOR Study. The publication/presentation strategy will be jointly developed by the Steering Committee and the Data Oversight Committee and enforced by the Data Oversight Committee.

- **Study Team**

  The Study Team consists of members of the Sponsor's staff from different disciplines to oversee the daily work of the C-TOR Study. External members of the Study Team come from CROs and other firms.

  - **Clinical Research Organizations (CROs)**

    Two CROs are in control of the identification of cases and controls, data collection, field monitoring and site management.

    Kendle International
    Stefan-George-Ring 6,
    D-81929 München, Germany

    Tel.: +49 89 9939130

    PRA International
    Dynamostr. 13-15,
    D-68165 Mannheim, Germany

    Tel.: +49 621 8782 513

    Kendle is also responsible for developing the Computer-Assisted Personal Interview (CAPI), the software for directly entering the questionnaire data into a laptop computer. PRA provides the dynamic web-based patient identification and reporting process and data management services. Dynarand, the developer of the DWS, is directed by PRA. Medical monitoring and site support are provided by PRA.

  - **Commercial Organizations and Academic Service Providers**

    A commercial organization is responsible for the development of the statistical analysis plan and for the analysis of the collected data.

Axio Research Corporation
2601 Fourth Avenue, Suite 200
Seattle, WA 98121, USA

Another commercial organization is responsible for the development of the DWS which will be used for coordinating, collecting and reporting administrative data.

Dynarand, LLC
55 Francisco, Suite 780
San Francisco, CA 94133, USA

University-affiliated service providers are responsible for the development, administration and validation of the C-TOR questionnaire, in addition staff from the Free University of Amsterdam train the interviewers and monitor the interviewer performance.

Department of Social Research Methodology
Vrije Universiteit
De Boelelaan 1081C
NL-1081 HV Amsterdam, The Netherlands

Department of Social Sciences and Department of Psychiatry
Vrije Universiteit
Valeriusplein 9
NL-1075 BG Amsterdam, The Netherlands

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Boston, United States

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Lone Star Oncology
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The University of Chicago
Chicago, United States

Prof. Arpad Somogyi
Pre-Accession Adviser EU-Twinning Project Food Safety Office
Ministry of Agriculture and Rural Development (MARD)
Budapest, Hungary

- **Study Sponsor**

  THE WEINBERG GROUP LLC of Brussels, Belgium is the C-TOR Study Sponsor and, as such, is responsible for management and data control in accordance with directives of the European Union and Belgium National Law. Financial support for this study is provided by Philip Morris International (PMI). PMI has no active involvement in the design or conduct of the study, however, the financial support will be recognized in all reports submitted for publication or otherwise made public, and the financial backer (PMI) will receive a copy of any publication or other release at the same time as the submission for publication or release is made.

  THE WEINBERG GROUP LLC
  360 Boulevard du Souverain
  B-1160 Brussels, Belgium

  Tel.: +32 2626 1170

- **Quality Assurance and Quality Control**

  The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems.

- **Study Administrative Support**

  In addition, the Sponsor will provide administrative support via the **Study Document Center** and the **Study Website.** All documents developed during the course of the C-TOR Study and approved by the Steering Committee will be stored and maintained at the Study Document Center. All C-TOR Study meeting minutes (except the minutes of the meetings of the Data Oversight Committee), presentations, publications, press releases and relevant literature will be archived. Approved documents important to be accessible by

various C-TOR Study groups will be made available on the Study Website.

APPENDIX C:
Screening Log

Screening Log — C-TOR Study

1. Please enter patient code (file code) used in your hospital to identify the patient for your own reference only! You will need this information to be able to identify your patient to be able to answer queries following the documentation but these data must not be forwarded to anybody outside the hospital.
2. Please enter the patient information into the respective columns from the patient file. The NUTS coding for the administrative area is provided by a separate sheet.
3. Also, please enter the outcome of your recruitment efforts into the "Reason for non-participation" column. To make it easier for you, please use the following codes (also located at the bottom of each sheet): 1 = selection criteria not met; 2 = Not willing to participate in a study supported by a tobacco company; 3 = Not willing to participate due to other reasons; 4 = not available (left hospital, died); 5 = unable to participate in the interview; 9 = other reason, please specify
4. After the completion of a sheet please date and sign the sheet. This screening log will then be copied and collected by the CRA during a monitoring visit. Please keep the original in your investigator files with the other study materials at your institution

Please make sure that no personal patient information leaves the hospital.

Screening Log — C-TOR Study

	In-house File Ref. No.	Identification date (dd/mm/yy)	Age (years)	Sex (M/F)	Admin. area of residence*	Admission diagnosis (ICD-10 Code)	Identification indicator (0= control,1= case)	Informed Consent Form signed? (Y/N)	Reason for not participating in Study**
1.									
2.									
3.									
4.									
5.									
6.									
7.									
8.									
9.									
10.									

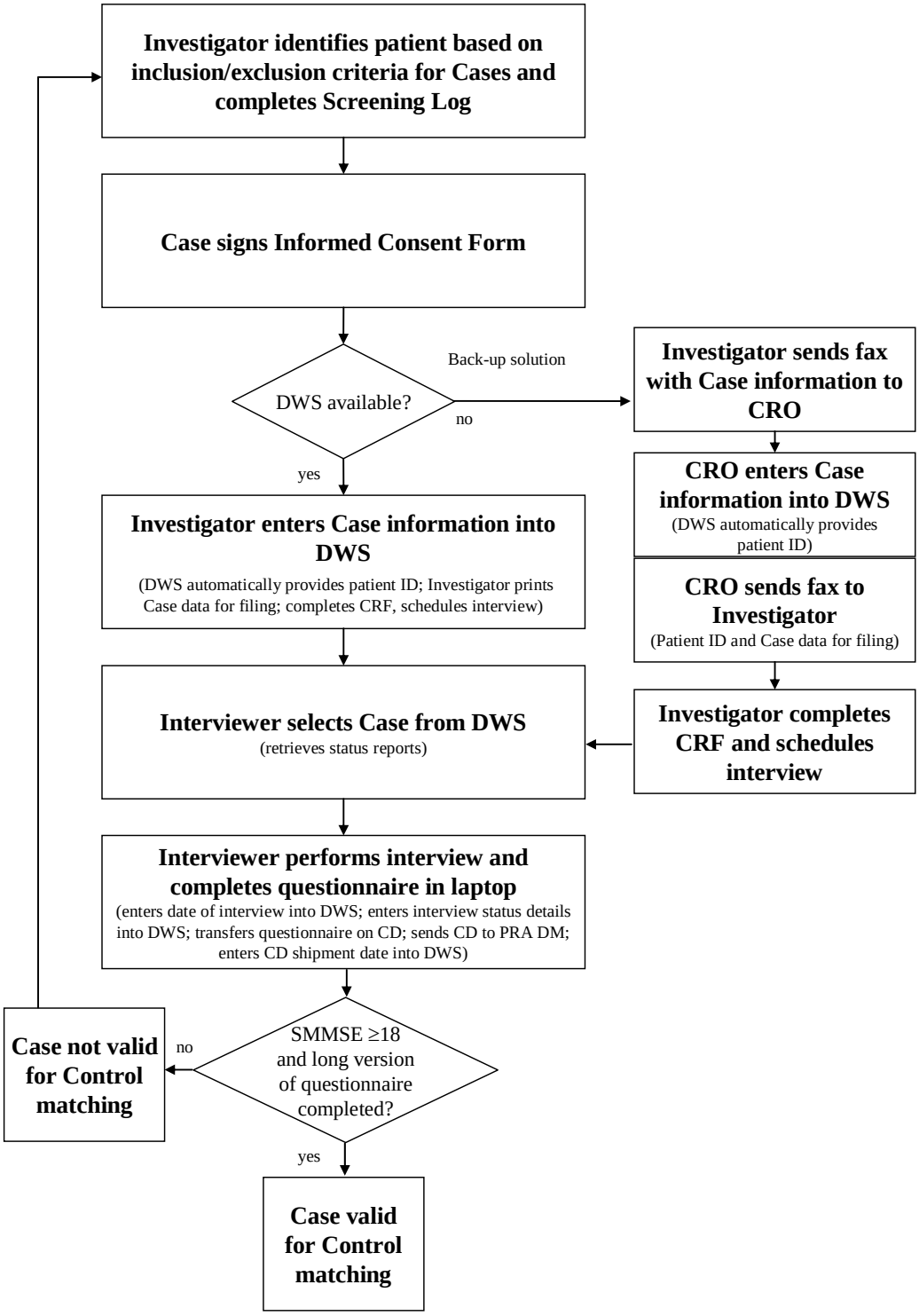
*** This is the area where the patient is living .See separate coding sheet for NUTS code (4 digits).**

** **1 = selection criteria not met; 2 = Not willing to participate in a study supported by a tobacco company; 3 = Not willing to participate due to other reasons; 4 = not available (left hospital, died); 5 = unable to participate in the interview; 9 = other reason, please specify**

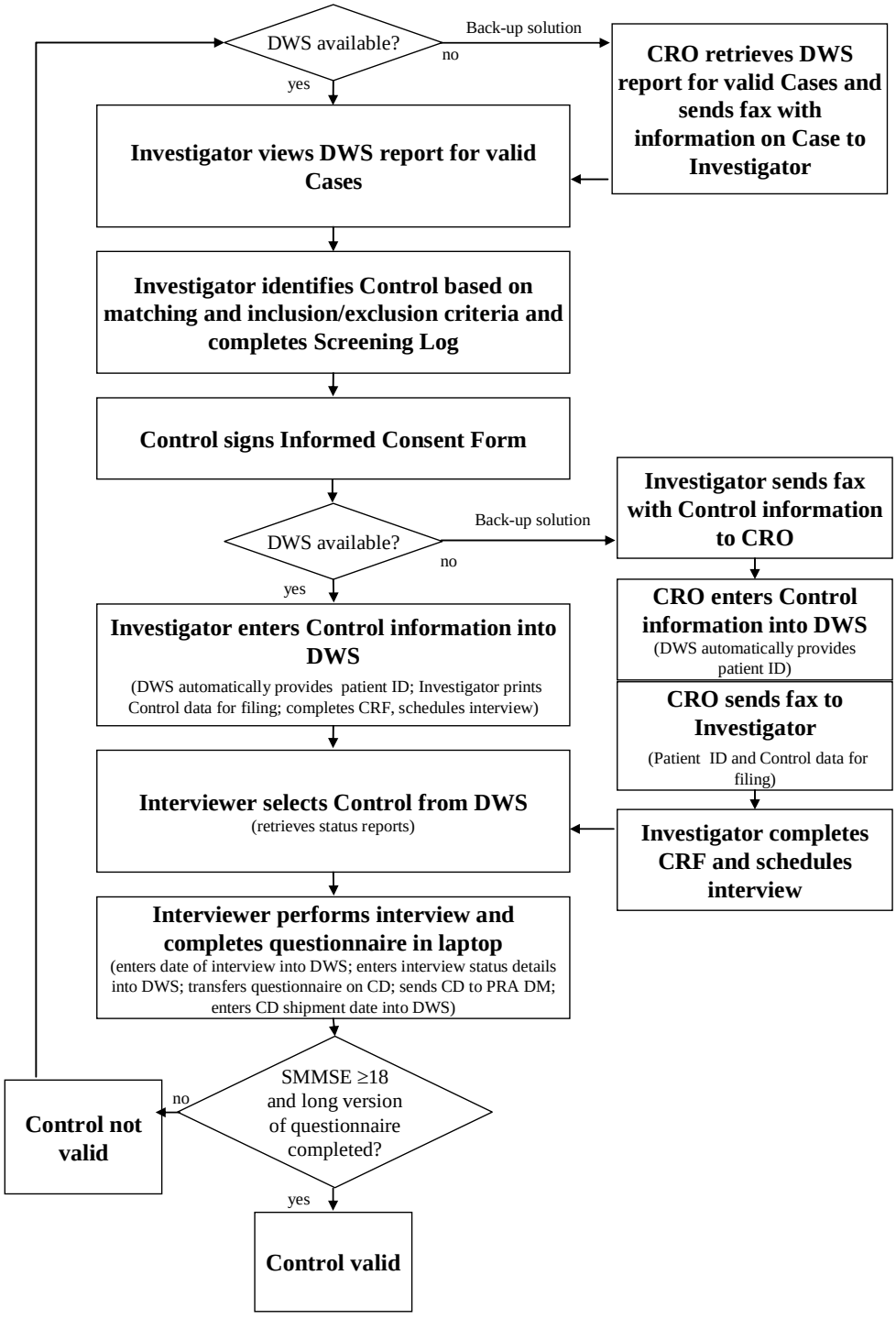
Date: _____ Site ID: _____ Investigator Signature: _____

Page __

APPENDIX D.1:
Case Identification Flowchart



APPENDIX D.2:
Control Identification Flowchart



APPENDIX E:
C-TOR Questionnaire

Case control study – Tobacco Overview of Risk (C-TOR)
Questionnaire

June 21, 2005

I. Introductory Questions

1. *Interview identification*

Site ID: _____
Interviewer ID: _____
Respondent ID: _____

2. *Date and time of interview*

Year: _____ [2004-2008]
Month: _____ [01-12]
Day: _____ [01-31]
Time: _____ [00-23:00-59]

3. *Gender of respondent*

○ male
○ female

4. *In what year and month were you born?*

Year: _____ [1900-1990]
Month: _____ [01-12]

<This information is used to set life event history calendar. Only age will be captured for data passage.>

5. *Can you please tell me the country and* [province/state/county] *in which you currently reside?*

Country:_____

Province/State/County_____

<Only information on administrative region for data passage.>

II. SMMSE Questions

6. Before starting with the interview, I would like to ask you some preliminary questions. You may find some of these questions very simple to answer, but others more difficult. They will tell me, however, if instead of a long interview, a set of different, much shorter questions are more suited for your situation.

6.1 **[Allow 10 seconds for each reply]**

a) *What year is this?*
[accept exact answer only] ☐ [0-1]

b) *What season is this?*
[during last week of the old season or first week of a new season, accept either season.] ☐ [0-1]

c) *What month of the year is this?*
[on the first day of new month, or last day of the previous month, accept either month] ☐ [0-1]

d) *What is today's date?*
[accept previous date or next date, e.g., on the 7th accept the 6th or 8th] ☐ [0-1]

e) *What day of the week is this?*
[accept exact answer only] ☐ [0-1]

6.2 **[Allow 10 seconds for each reply]**

a) *What country are we in?*
[accept exact answer only] ☐ [0-1]

b) *What province/state/county are we in?*
[accept exact answer only] ☐ [0-1]

c) *What city/town are we in?*
[accept exact answer only] ☐ [0-1]

d) [In clinic/hospital]
What is the name of this hospital/building?
[accept exact name of hospital or institution only] ☐ [0-1]

[In home]
What is the street address of this house?
[accept street name and house number or equivalent in rural areas]

e) [In clinic/hospital]
What floor of the building are we on now?
[accept exact answer only] ☐ [0-1]

[In home]
What room are we in?
[accept exact answer only]

6.3 *I am going to name 3 objects. After I have said all three objects, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.* ☐ [0-3]

[say them slowly at approximately 1 second intervals]

Ball Car Man

Please repeat the 3 items for me.

[Score 1 point for each correct response on the first attempt. Allow 20 seconds for the response. If the respondent did not repeat all 3, repeat the 3 words until they are learned or up to a maximum of 5 times.]

6.4 *Spell the word "WORLD"* [0-5]
[you may help the respondent to spell "world" correctly]

Now spell it backwards please.

[Allow 30 seconds to spell backwards. If the respondent cannot spell backwards - even with assistance - score 0]
[Type the backwards spelled word here as spelled by the respondent:
The score will automatically be entered after you press "Enter".]

6.5 *Now what were the 3 objects that I asked you to remember?* [0-3]

Ball Car Man
[Score 1 point for each correct response regardless of order, allow 10 seconds.]

6.6 [Show wristwatch on respondent's screen. Ask:]

What is this called?

[Allow 10 seconds. Score 1 point for correct response. Accept "wristwatch" or "watch". Do not accept "clock", "time", etc.]

6.7 [Show pencil on respondent's screen. Ask:] [0-1]

What is this called?

[Score 1 point for correct response. Accept "pencil" only – score 0 for pen]

6.8 I'd like you to repeat the following phrase after me: [0-1]

No ifs, ands or buts

[Allow 10 seconds for response. Score 1 point for a correct repetition. Must be exact and complete, e.g., "No ifs or buts" - score 0]

6.9 *Read the words on your screen and then do what it says.* [0-1]

[Press button to show the words on the respondent's screen]

Show "Close your eyes"

[If the respondent just reads and does not then close [his/her] eyes, then repeat original instructions: "Read the words on the screen and then do what it says." You may repeat the instructions a maximum of 3 times. Allow 10 seconds, score 1 point only if the respondent closes eyes. The respondent does not have to read the words on the screen aloud.]

6.10 *Are you right- or left-handed?* ○ right-handed ○ left-handed

[Take a piece of paper and hold it up in front of the respondent. Say:] ☐ [0-3]

[If respondent is right-handed:]

Take this paper in your left hand, fold the paper in half once with both hands and put the paper down on your lap.

[If respondent is left-handed:]

Take this paper in your right hand, fold the paper in half once with both hands and put the paper down on your lap.

[Takes paper in correct hand: 1 point

Folds it in half: 1 point

Puts it on lap: 1 point

Allow 30 seconds. Score 1 point for each instruction correctly executed.]

6.11 [Hand respondent a pencil and paper] ☐ [0-1]

Write any complete sentence on that piece of paper.

[Allow 30 seconds. Score 1 point. The sentence should make sense. Ignore spelling errors.]

6.12 [Place pencil, eraser and paper in front of the respondent. Press button to show picture on the respondent's screen. Say:] ☐ [0-1]

Copy this design please

Show picture

[Allow multiple tries until the respondent is finished and hands the paper back. Score 1 point for correctly copied diagram. The respondent must have drawn a 4-sided figure between two 5-sided figures. Maximum time allowed is 1 minute.]

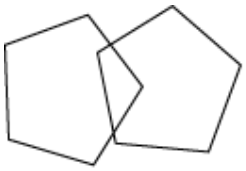
Score picture

Total score:

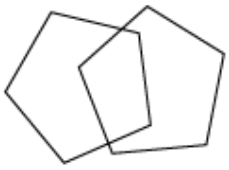
Scoring the figure

The respondent must draw two 5-sided figures intersected by a 4-sided figure

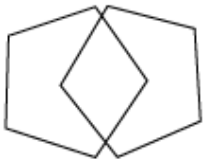
CORRECT
Score 1



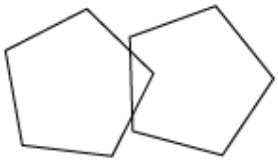
INCORRECT
Score 0



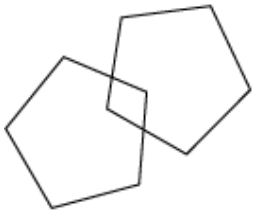
CORRECT
Score 1



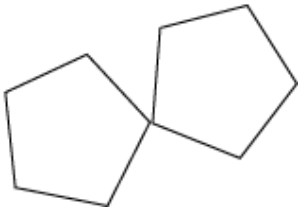
INCORRECT
Score 0



CORRECT
Score 1



INCORRECT
Score 0



Score: [0-1]

OK

Adapted from: Molloy, D.W., et al. 1991. Reliability of a Standard Mini-Mental State Examination compared with the traditional Mini-Mental State Examination. Am. J. Psychiatry. 148:102-105.

[If the respondent scores 18 or more, proceed to Section III. Life Event History Calendar Questions.

If the respondent scores 17 or less, proceed to the short version of the questionnaire (Section IV).]

III. Life Event History Calendar Questions

Landmark Events Domain

In order to help establish a solid timeline for the respondent and aid them in the recall of autobiographical events, a prefixed landmark events timeline will be developed. This timeline will provide general events, (e.g., World War II, the Kennedy Assassination) as well as country-specific events.

Residence Domain

1. Address Timeline

Introductory Script

Let's start with the places where you have lived. I would like to know where you have lived over your entire lifetime and when you lived in each place.

Can you tell me the street name of each of the places where you have lived and when you lived there?

You can start with the first place at which you lived, or you may want to think of where you are living now and work backwards in time.

You may have been too young to remember some moves, but you may know about them from what other family members have told you.

<Only information of the time interval and residence number (i.e., residence 1, residence 2) for data passage. All other information used only for cueing.>

2. Setting Timeline

Introductory Script

For each place where you have lived, can you please tell me the setting in which you have lived? Would you say you lived in:

a farm or a home in the countryside;
a country village;
a town or a small city;
the suburbs or outskirts of a big city; or
a big city?

Let's start when you lived in [place].

Did it change in character while you were living there?

Response Alternatives

- Farm or home in the countryside
- Country village
- Town or small city
- Suburbs of a big city
- Big city
- Other
- Not applicable
- Don't know
- Refused

[For each place:]

Would you say it was:

a densely populated area,

a sparsely populated area, or

an intermediate area that was neither densely or sparsely populated?

Did it change in character while you were living there?

Response Alternatives

- Densely populated
- Intermediate area
- Sparsely populated
- Not applicable
- Don't know
- Refused

Life Events Domain

3. Marriage and Marriage Events Timeline

Introductory Script

Now I'd like to ask you a few questions about marriage. Have you ever been married, [including a registered partner relation when applicable]*?*

[If yes:] *How many times were you married? Can you please provide the first name(s) or initial(s) of your spouse(s), and when you were married to them* [or entered into a registered partner relation]?

[For each spouse:] *Can you tell me if you ever permanently separated from [name or initial], and whether there was a divorce, or if you were widowed? In what year?*

<Only information of the time interval and spouse number (i.e., spouse 1, spouse 2) for data passage. All other information used only for cueing.>

Response Alternatives

- Separation
- Divorce
- Widowhood
- Other
- Don't know
- Refused

4. Partner(s) Timeline

Introductory Script

Have you ever lived with a partner as if married?

[If yes:] *Can you please provide the first name(s) or initial(s) of all of the partners with whom you have lived, and tell me when you were living with them as if married?*

<Only information of the time interval and partner number (i.e., partner 1, partner 2) for data passage. All other information used only for cueing.>

5. Births, Adoptions, and Foster Children Timeline

Introductory Script

Do you have any children, including adopted, step or foster children? Please tell me their first names or initials and when they were born or came to live with you.

<Only information of the time interval and child number (i.e., child 1, child 2) for data passage. All other information used only for cueing.>

Response Alternatives

- Birth
- Adopted
- Step
- Foster
- Other
- Don't know
- Refused

6. Death of Important Persons Timeline

<Information captured in this timeline is not for data passage – only to be used for cueing.>

Are there any persons, like parents, children, other family members or friends whose death had a significant impact on your life? Can you please tell me in what year they died?

Response Alternatives

- Father
- Mother
- Child (including adopted, step, foster children)
- Brother (including step brother, etc.)
- Sister (including step sister, etc.)
- Grandfather
- Grandmother
- Friend
- Other
- Don't know
- Refused

7. Persons Living in Private Or Public Dwellings Timeline

Introductory Script

*I am also interested in how many people, **including yourself**, were living in the same household as you.*

Please include both family members, and non-family members.

When did the number of persons living in the same household change?

If you lived in a public institution such as barracks, boarding school, monastery or convent, or the like, please tell me about this as well. You do not have try to estimate the number of people that lived there.

[Should the respondent have questions about the makeup of the household:]

I am interested in the people with whom you shared the same accommodation (such as a house, apartment or flat in a building, etc.) and common living arrangement. By living arrangement, I mean people in the household who shared in the expenses of the household, had meals together, or shared a room. Sharing in expense also includes those who benefited from the household expenses, such as children or persons with no income who lived in the household.

Number of Household Members Response Alternatives

- 1
- 2
- 3
- 4
- 5
- 6
- More than 6
- Public institution
- Don't know
- Refused

8. Residential Smoking Timeline

Introductory Script

*Now, I am interested in learning whether any smokers, **excluding yourself**, lived in the same household as you at any point in your life?*

Does or did your parents, siblings, children, spouse(s) or partner(s) smoke while you were living with them? **[If yes:]** *Which years was that?*

Did other people living with you smoke?

<The response alternatives below should be shown on the respondent's screen. However, what will be captured for data passage is the actual number of household members that smoked.>

Response Alternatives

- No
- Mother smokes or smoked
- Father smokes or smoked
- Spouse/Partner smokes or smoked
- Child(ren) smokes or smoked
- Other household member smokes or smoked
- Lived in public institution
- Don't know
- Refused

Education Domain

9. Schools Timeline

Introductory Script

(Country-specific questions, response alternatives and coding corresponding to ISCED-97 to be provided. Country-specific fill variables will be used to compute ISCED-97 categories. Note that while there are six basic ISCED level there will be X number of response variables, depending on the country.)

I am now interested in any formal schooling that you have had over your entire lifetime. Please tell me about those periods in which you were attending <schooling type country fill for primary education or first stage of basic education (ISCED-97, Level 1)>, <schooling type country fill lower secondary education or second stage of basic education (ISCED-97, Level 2)>, <schooling type country fill for upper secondary education (ISCED-97, Level 3)>, or <schooling type country fill for post-secondary, non-tertiary education (ISCED-97, Level 4)>.

In addition, I would like to know if you attended <schooling type country fill for first stage of tertiary education (not leading directly to an advanced research qualification (ISCED-97, Level 5)>, and <schooling type country fill for vocational education (ISCED-97, sub-categories for levels 2, 3, and 4)> and <schooling type country fill for second stage of tertiary education (leading directly to an advanced research qualification (ISCED-97, Level 6)>.

Response Alternatives

- No formal schooling
- *<schooling type country fill for primary education or first stage of basic education (ISCED-97, Level 1)>*
- *<schooling type country fill lower secondary education or second stage of basic education (ISCED-97, Level 2)>*
- *<schooling type country fill lower for ISCED-97, Level 2 subcategories>*
- *<schooling type country fill for upper secondary education (ISCED-97, Level 3)>*
- *<schooling type country fill upper secondary for ISCED-97, Level 3 subcategories>*
- *<schooling type country fill for post-secondary, non-tertiary education (ISCED-97, Level 4)>*
- *<schooling type country post-secondary for ISCED-97, Level 4 subcategories>*
- *<schooling type country fill for first stage of tertiary education (not leading directly to an advanced research qualification (ISCED-97, Level 5)>*
- *<schooling type country fill for second stage of tertiary education (leading directly to an advanced research qualification (ISCED-97, Level 6)>*
- Don't know
- Refused

10. Degrees Timeline

Introductory Script

(Country-specific questions, response alternatives and coding corresponding to ISCED-97 to be provided. Country-specific fill variables will be used to compute ISCED-97 categories. Note that while there are six basic ISCED level there will be X number of response variables, depending on the country.)

What is the highest educational level you have completed? [Show response alternatives on respondent's screen.]

Response Alternatives

- *Did not complete primary (compulsory) education*
- *Primary education or first stage of basic education*
- *Lower secondary education or second stage of basic education*
- *Upper secondary education*
- *Post-secondary, non-tertiary education*
- *First stage of tertiary education (not leading directly to an advanced research qualification)*
- *Second stage of tertiary education (leading directly to an advanced research qualification)*
- *Don't know*
- *Refused*

Occupation Domain

11. Employer Timeline

<Information captured in this timeline is not for data passage – only to be used for cueing.>

Introductory Script

Now I would like to ask you about your work for pay, including any work you have done for employers, any military service you may have had, or any self-employment.

Have you ever worked for pay at one job for 3 months or more?

[If yes:] *Could you please tell me the names of the main employers who you have worked for, and when you worked for them?* [In this case, the main employer is the employer that yielded the most income during the time period.]

If you worked as a homemaker in your own household, please let me know that as well.

Response Alternatives

- Input information on employer name. Military and homemaker should also be entered into the employer name field.

12. Occupational Exposure Timeline

Introductory Script

Have you ever worked in any of the following professions or industries even for a short period of time?

Please consider the categories carefully. If yes, I would like you to tell me when that was and for how long.

[If the respondent answers **yes** to any of the occupation/industry choices, interviewer should cycle through all employers.]

Response Alternatives for Each of the Following Occupations

- Yes
- No

Response Alternatives for Occupations

- Pesticide production or application
- Roofer or asphalt worker
- Beryllium refining
- Coke plant
- Painter
- Asbestos production
- Welder
- Gas worker
- Construction industry
- Arsenic mining
- Iron ore mining
- Zinc-lead mining
- Asbestos mining
- Talc mining
- Gold mining
- Uranium mining
- Other mining
- Haulier or truck/bus driver
- Garage/service station
- Production of chloromethylether
- Printing industry
- Rubber industry
- Production of chromate pigments
- Leather industry
- Production of batteries
- Cadmium smelting
- Copper smelting
- Laundry or dry cleaning
- Chromium plating
- Ferrochromium production
- Man-Made Mineral Fibres Industry: Glasswool, Rockwool, Continuous Filament or Other
- Iron or steel foundry
- Production of aluminium
- Butcher
- Nickel refining
- Chimney sweep
- Production of mustard gas
- Don’t know
- Refused

13. Others Smoking In Workplace Timeline

Introductory Script

Did you work indoors or outdoors?

[If indoors:] *To what extent were you exposed to other people's smoking while at your workplace?*

Would you say:

daily,

several times a week,

once a week,

several times a month,

once a month,

less than once a month, or

not at all?

Response Alternatives

- Worked outdoors
- Daily
- Several times a week
- Once a week
- Several times a month
- Once a month
- Less than once a month
- Not at all
- Don't know
- Refused

Smoking History Domain

14. Smoking History Timeline

Introductory Script

Have you ever smoked 100 or more cigarettes in your entire lifetime?

Response Alternatives:
- Yes (move to following question)
- No (proceed to "Other tobacco timelines")
- Don't Know (proceed to "Other tobacco timelines")
- Refused (proceed to "Other tobacco timelines")

Did you smoke 100 or more cigarettes between [two years from date of execution of the informed consent and following 12 months]?

Response Alternatives:
- Yes
- No
- Don't Know
- Refused

I would like for you to review your life and the periods in your life when you were smoking and periods where you did not smoke. A smoking period refers to any period in which you smoked 100 or more cigarettes per year.

How old were you when you first started smoking?

Do you still smoke?

Response Alternatives:

- Smoking (100 or more cigarettes per year)
- Non-smoking

15. Cigarette Brand and Amount Smoked Timeline

Introductory Script

I would now like to ask you more specific details about the brands of cigarettes you smoked and the amount you smoked of each of these brands.

If you were not smoking manufactured cigarettes, but were rolling your own, I would like to know this too.

When you first started smoking, can you remember what brand you smoked and how much? To help you remember, I would like to show you a selection of the most popular brands smoked at that time. [Show the brand response cards and record the brand identified. If the time interval is after 1979, use the response card and the image database as it is especially important to determine the exact brand used.]

[For each brand identified:] *Was this the package?*

Were the cigarettes filtered or unfiltered?

How much did you smoke of [brand name]*?*

You can answer how many cigarettes or how many packs per day, or per week, per month or per year, on average you smoked, which ever you prefer.

If you only smoked on special occasions, such as a party or a birthday, please tell me.

Did you smoke any other cigarette brands during this time? **[If yes:** Show the response cards of cigarette brands and make use of the image database].

Again, can you tell me how much you smoked of [brand name]? [Repeat this line of questioning until the smoking history timeline is completed for a smoking interval and then start again at the next smoking interval – do not ask for more than 3 brands smoked simultaneously in any one time interval.]

Response Alternatives

- Show brand cards and make use of the image database
- Ask if the brand used was filtered or unfiltered
- Enter the amount for cigarettes or packs
- Ask frequency of cigarette use

Frequency of Use Response Alternatives

- Day
- Week
- Month
- Year
- Don't know
- Refused

16. Other Tobacco Timelines

16.1 Cigar Timeline

Introductory Script

Have you ever smoked 100 or more cigars in your entire lifetime?

Response Alternatives:
- Yes (move to following question)
- No (proceed to question 16.2)
- Don't Know (proceed to question 16.2)
- Refused (proceed to question 16.2)

Did you smoke 100 or more cigars between [two years from date of execution of the informed consent and following 12 months]?

Response Alternatives:
- Yes (move to following question)
- No (proceed to question 16.2)
- Don't Know (proceed to question 16.2)
- Refused (proceed to question 16.2)

In which years did you regularly smoke cigars?

16.2 Pipe Timeline

Introductory Script

Did you ever smoke a pipe 100 or more times in your entire lifetime?

Response Alternatives:
- Yes (move to following question)
- No (proceed to question 16.3)
- Don't Know (proceed to question 16.3)
- Refused (proceed to question 16.3)

Did you smoke a pipe 100 or more times between [two years from date of execution of the informed consent and following 12 months]?

Response Alternatives:
- Yes (move to following question)
- No (proceed to question 16.3)
- Don't Know (proceed to question 16.3)
- Refused (proceed to question 16.3)

In which years did you regularly smoke a pipe?

16.3 Cigarillos Timeline

Introductory Script

Have you ever smoked more than 100 cigarillos?

Response Alternatives:
- Yes (move to following question)
- No (proceed to question 16.4)
- Don't Know (proceed to question 16.4)
- Refused (proceed to question 16.4)

In which years did you regularly smoke cigarillos?

16.4 Chewing Tobacco/Snuff Timeline

Introductory Script

Did you ever use chewing tobacco or snuff more than 100 times?

Response Alternatives:
- Yes (move to following question)
- No (proceed to question 17)
- Don't Know (proceed to question 17)
- Refused (proceed to question 17)

In which years did you regularly use chewing tobacco or snuff?

Health Domain

17. Diet – Health Timeline

Introductory Script

At different points in their lives, people may change their diets because of health reasons, a change in their financial situation or other factors.

Please consider the five different categories on your screen that may have applied to you at different times during your life and tell me which category described your diet best during a particular period. According to present standards,

you almost always ate unhealthy foods,

you usually ate unhealthy foods,

you ate unhealthy and healthy foods about equally,

you usually ate healthy foods, or

you almost always ate healthy foods.

I would like you to start when you were age 13, if possible.

Response Alternatives

- Almost always ate an unhealthy diet
- Usually ate an unhealthy diet
- Ate an unhealthy and healthy diet about equally
- Usually ate a healthy diet
- Almost always ate a healthy diet
- Don't know
- Refused

18. Diet – Fruits and Vegetables Timeline

Introductory Script

At different points in their lives, people may eat diets that are:

high in fruits and vegetables,

moderate in fruits and vegetables, or

low in fruits and vegetables.

How about you?

I would like you to start when you were age 13, if possible.

Response Alternatives

- Low
- Moderate
- High
- Don't know
- Refused

19. Diet – Fatty Foods Timeline

Introductory Script

At different points in their lives, people may eat diets that are:

high in fatty foods,

moderate in fatty foods, or

low in fatty foods.

By fatty foods, I mean such foods as cheese, fatty cuts of meat, whole milk, butter and margarine, cookies and cakes, and the use of oils and margarine in foods.

Please indicate, since at least age 13, whether you had diets high in fatty foods, moderate in fatty foods, or low in fatty foods.

Response Alternatives

- Low
- Moderate
- High
- Don't know
- Refused

20. Alcohol Use Timeline

Introductory Script

Did you ever consume more than 100 alcoholic beverages in your entire lifetime?

[If yes:] *How old were you when you started to drink alcohol?*

When you started, how many alcoholic beverages did you drink per day or week?

Did that change? When?

How many drinks then?

Response Alternatives

- Use the reported alcoholic beverage numbers as the beginning and ending endpoints of intervals.

Frequency of Use Response Alternatives

- Day
- Week
- Month
- Year
- Don't know
- Refused

21. Weight Timeline

Introductory Script

Now, I'd like to ask you about your weight.

Please consider the five different categories on your screen that may have applied to you at different times during your life, and tell me which category described your weight best at a particular period. Don't count extra weight during your pregnancy.

Were you:

very overweight,

slightly overweight,

just right,

slightly underweight, or

very underweight?

Response Alternatives

- Very overweight
- Slightly overweight
- Just right
- Slightly underweight
- Very underweight
- Don't know
- Refused

Medical History Domain

22. Chronic Lung Disease Timeline

Introductory Script

Has a doctor ever told you that you have any of the following respiratory, breathing or lung diseases?

Please take a look at the different types on your screen, and tell me the type.

In what year did a doctor tell you that you have [specific type]?

[Mention each type, ask whether or not it was diagnosed, and, if yes, in what year.]

Types

- **Chronic Bronchitis** (inflammation of the lungs' airways)
- **Chronic Obstructive Lung Disease** (lung disorder in which the flow of air in and out of the lungs is poor or impaired)
- **Asthma** (breathing disorder in which there is wheezing and difficult breathing; a lung disease associated with tightening of the air passages)
- **Pneumonia** (an infection involving the lungs)
- **Tuberculosis**
- **Asbestosis** (lung disease caused by inhaling asbestos)
- **Silicosis** (lung disease caused by inhaling silica dust; also known as stone mason's disease)
- **Pneumoconiosis** (lung disease caused by inhaling mineral or metallic particles such as coal dust; also known as miner's lung or black lung)
- **Collapsed Lung**
- **Emphysema** (a disorder in which too much air collects deep in the lungs; a destructive lung disease characterized by large damaged airspaces and poor air exchange)
- **Other Respiratory, Breathing Or Lung Disease**– Please specify

23. Vascular Disease Timeline

Introductory Script

Has a doctor ever told you that you have any of the following vascular (blood vessel) diseases?

Please take a look at the different types on your screen, and tell me the type.

In what year did a doctor tell you that you have [specific type]?

[Mention each type, ask whether or not it was diagnosed, and, if yes, in what year.]

Types

- **Stroke** (blockage of a blood vessel to the brain, resulting in nerve cell death)
- **Hypertension** (high blood pressure)
- **Pulmonary Embolism** (blood clot in the lungs; blockage of an artery to the lungs by a clot or other material)
- **Thrombosis** (blood clotting within the blood vessels)
- **Poor Circulation** (low blood flow)

24. Coronary or Heart Disease Timeline

Introductory Script

Has a doctor ever told you that you have any of the following coronary or heart diseases? *Please take a look at the different types on your screen, and tell me the type.* *In what year did a doctor tell you that you have* [specific type]? [Mention each type, ask whether or not it was diagnosed, and, if yes, in what year.]

Types

- **Myocardial Infarction** (heart attack)
- **Heart Failure** (poorly functioning heart that is unable to maintain normal blood flow)
- **Angina** (chest pain due to decreased oxygen being supplied to the heart)
- **Pericarditis** (inflammation of the two-layer sack of tissue around the heart)
- **Infections of the Heart**
- **Arrhythmias** (irregular heart beat)
- **Valve Disease** (abnormality of a heart valve)
- **Rheumatic Heart Disease** (damage caused to the heart by rheumatic fever)
- **Congenital Heart Disease** (heart disease present at birth)

25. Cancer Timeline

Introductory Script

Has a doctor ever told you that you have any of the following types of cancer? *Please take a look at the different types on your screen, and tell me the type.* *In what year did a doctor tell you that you have* [specific type]? [Mention each type, ask whether or not it was diagnosed, and, if yes, in what year.]

Types

- Lung
- Breast
- Colon
- Rectum
- Esophagus
- Stomach
- Pancreas
- Bladder
- Ovary
- Lymphoma
- Leukemia
- Brain
- Kidney
- Liver
- Head and Neck
- Malignant Melanoma
- Cervix
- Other Cancer– Please specify

26. Diabetes Timeline

Introductory Script

Has a doctor ever told you that you have any of the following high blood sugar or diabetes-related diseases? *Please take a look at the different types on your screen, and tell me the type.* *In what year did a doctor tell you that you have* [specific type]? [Mention each type, ask whether or not it was diagnosed, and, if yes, in what year.]

Types

- **Diabetes** (condition in which blood sugar is too high)
    - **Insulin-Dependent Diabetes Mellitus** (type 1 diabetes; a condition in which blood sugar can only be controlled by insulin therapy injection)
    - **Noninsulin-Dependent Diabetes Mellitus** (type 2 diabetes; a condition in which blood sugar can be controlled by diet or drug therapy without needing insulin injection)
- **Neuropathy** (damage to the nerves, often inflammatory or degenerative; a disturbance in the function of the brain or spinal cord that may affect the nerves and muscles)
- Abnormal physical sensations such as numbness, tingling, burning sensation, prickling or itching that were related to high blood sugar

Socio-economic Domain (not life events based)

We also want to obtain general background information in this study. For that reason, I would now like to ask you some questions on income and education. We may have touched upon some of this information already, but we need to be certain that the information that we have is correct. Again, I would like to point out to you that all information that we obtain from you is strictly confidential and will not be passed on to others.

27 Income

Income is defined as wages or salaries; income from self-employment or farming; income from benefits such as a private, old age, or state pension; income from unemployment or redundancy benefits; income from investments, savings, insurance, or property; alimony; income from let lodging; or other financial or social assistance.

27.1 *Earlier in the interview, we discussed the members of your household. Do any of the current members of your household have an income of their own?*

- *Yes*
- *No*
- *Refused*
- *Don't know*

27.2 *On your screen you will see a number of answer categories. Will you please tell me what category applies to your household's net income a month? Please consider the contributions to the household income from all current household members and any other income which may be received by the household as a whole.*

[Net income is income after deductions of business expenses, income tax, national insurance or pension payments, or any other compulsory deductions.]

(For study countries in which the euro is not in use, country specific monetary values corresponding to these euro values will be developed.)

- *0-1000 euro*
- *1001-1500 euro*
- *1501-2000 euro*
- *2001-3000 euro*
- *3001-4000 euro*
- *4001-5000 euro*
- *5001+*
- *Refused*
- *Don't know*

27.3 *Which of the following descriptions on the screen comes closest to how you view your household's income?*

- *Living comfortably on present income*
- *Coping on present income*
- *Finding it difficult on present income*
- *Finding it very difficult on present income*
- *Don't know*
- *Refused*

28 Employment status respondent

Earlier in the interview, I asked you some questions on employment. The next questions are just to be certain that we understand your employment situation for the majority of the last five years.

28.1 *On your screen you will see a number of situations.*

Within the last five years, what would best characterize your employment status?

More than one category may apply.

- *Employed full-time*
- *Employed part-time*
- *Temporarily out of work*
- *Helping family member*
- *Not in labour force*
- *Unemployed*
- *Student/In school/In vocational training*
- *Retired*
- *Homemaker/Home duties*
- *Permanently disabled*
- *Refused*
- *Don't know*

28.2 *Please consider your entire working life. Can you tell me what was your main occupation for the majority of your life?*

[Type the occupation given by the respondent.]

28.3 *Did you ever, in your working life, have a job in which you supervised the work of other employees?*

- *Yes*
- *No*
- *Refused*
- *Don't know*

29 Employment status partner/spouse

Within the last five years, which member of your household has been the main source of household income?

- *Respondent*
- *Partner/Spouse*
- *Respondent and Partner/Spouse about equal*
- *Other member(s) of household*
- *Refused*
- *Don't know*

29.1 *On your screen you will see a number of situations regarding employment.*

Within the last five years, what would best characterize your [most recent/current] [partner's/spouse's] *employment status?*

More than one category may apply.

- *Employed full-time*
- *Employed part-time*
- *Temporarily out of work*
- *Helping family member*
- *Not in labour force*
- *Unemployed*
- *Student/In school/in vocational training*
- *Retired*
- *Homemaker/Home duties*
- *Permanently disabled*
- *Not applicable*
- *Refused*
- *Don't know*

29.2 *Did your* [most recent/current] [partner/spouse] *ever, in* [his/her] *entire working life, have a job in which* [he/she] *supervised the work of other employees?*

- *Yes*
- *No*
- *Refused*
- *Don't know*

30 *Earlier in the interview, I asked you some questions on education. The next questions are about the education of your* [current/most recent] [partner/spouse] *and your parents.*

30.1 Education partner/spouse

What is the highest level of education that your [current/most recent] [partner/spouse] *completed?*

On your screen you will see a number of categories.

Will you please tell me what category applies to your partner?

- *Did not complete primary (compulsory) education*
- *Primary education or first stage of basic education*
- *Lower secondary education or second stage of basic education*
- *Upper secondary education*
- *Post-secondary, non-tertiary education*
- *First stage of tertiary education (not leading directly to an advanced research qualification)*
- *Second stage of tertiary education (leading directly to an advanced research qualification)*
- *Don't know*
- *Refused*

30.2 Education father

What is the highest level of education that your father completed?

On your screen you will see the same categories as before.

Please tell me what category applies to your father.

- *Did not complete primary (compulsory) education*
- *Primary education or first stage of basic education*
- *Lower secondary education or second stage of basic education*
- *Upper secondary education*
- *Post-secondary, non-tertiary education*
- *First stage of tertiary education (not leading directly to an advanced research qualification)*
- *Second stage of tertiary education (leading directly to an advanced research qualification)*
- *Don't know*
- *Refused*

30.3 Education mother

What is the highest level of education that your mother completed?

On your screen you will see the same categories as before.

Please tell me what category applies to your mother.

- *Did not complete primary (compulsory) education*
- *Primary education or first stage of basic education*
- *Lower secondary education or second stage of basic education*
- *Upper secondary education*
- *Post-secondary, non-tertiary education*
- *First stage of tertiary education (not leading directly to an advanced research qualification)*
- *Second stage of tertiary education (leading directly to an advanced research qualification)*
- *Don't know*
- *Refused*

31. Closing

[End of interview]

(To be handled in interviewer training)

IV. Short Questionnaire

For this study, we want to obtain general background information. For that reason, I would now like to ask you some questions on your income, occupation, and education. I would like to point out that all information that we obtain from you is strictly confidential and will not be passed on to others.

1 Income

Income is defined as wages or salaries; income from self-employment or farming; income from benefits such as a private, old age, or state pension; income from unemployment or redundancy benefits; income from investments, savings, insurance, or property; alimony; income from let lodging; or other financial or social assistance.

1.1 *Do any of the current members of your household have an income of their own?*

- *Yes*
- *No*
- *Refused*
- *Don't know*

1.2 *On your screen you will see a number of answer categories. Will you please tell me what category applies to your household's net income a month? Please consider the contributions to the household income from all current household members and any other income which may be received by the household as a whole.*

[Net income is income after deductions of business expenses, income tax, national insurance or pension payments, or any other compulsory deductions.]

(For study countries in which the euro is not in use, country specific monetary values corresponding to these euro values will be developed.)

- *0-1000 euro*
- *1001-1500 euro*
- *1501-2000 euro*
- *2001-3000 euro*
- *3001-4000 euro*
- *4001-5000 euro*
- *5001+*
- *Refused*
- *Don't know*

1.3 *Which of the following descriptions on the screen comes closest to how you view your household's income?*

- *Living comfortably on present income*
- *Coping on present income*
- *Finding it difficult on present income*
- *Finding it very difficult on present income*
- *Don't know*
- *Refused*

2 Employment status respondent

2.1 *On your screen you will see a number of situations.*

Within the last five years, what would best characterize your employment status?

More than one category may apply.

- *Employed full-time*
- *Employed part-time*
- *Temporarily out of work*
- *Helping family member*
- *Not in labour force*
- *Unemployed*
- *Student/In school/In vocational training*
- *Retired*
- *Homemaker/Home duties*
- *Permanently disabled*
- *Refused*
- *Don't know*

2.2 *Please consider your entire working life. Can you tell me what was your main occupation for the majority of your life?*

[Type the occupation given by the respondent.]

2.3 *Did you ever, in your working life, have a job in which you supervised the work of other employees?*

- *Yes*
- *No*
- *Refused*
- *Don't know*

3 Employment status partner/spouse

Within the last five years, which member of your household has been the main source of household income?

- *Respondent*
- *Partner/Spouse*
- *Respondent and Partner/Spouse about equal*
- *Other member(s) of household*
- *Refused*
- *Don't know*

3.1 *Have you ever been married or lived with a partner as if married?*

- *Yes*
- *No*
- *Refused*
- *Don't know*

<[If yes:] Proceed to question 3.2. [If no, don't know, refused:] Proceed to question 4.>

3.2 *On your screen you will see a number of situations regarding employment.*

Within the last five years, what would best characterize your [most recent/current] [partner's/spouse's] *employment status?*

More than one category may apply.

- *Employed full-time*
- *Employed part-time*
- *Temporarily out of work*
- *Helping family member*
- *Not in labour force*
- *Unemployed*
- *Student/In school/in vocational training*
- *Retired*
- *Homemaker/Home duties*
- *Permanently disabled*
- *Not applicable*
- *Refused*
- *Don't know*

3.3 *Did your* [most recent/current] [partner/spouse] *ever, in* [his/her] *entire working life, have a job in which* [he/she] *supervised the work of other employees?*

- *Yes*
- *No*
- *Refused*
- *Don't know*

4. *What is the highest educational level you have completed?*

On your screen you will see a number of categories.

Will you please tell me what category applies to you?

- *Did not complete primary (compulsory) education*
- *Primary education or first stage of basic education*
- *Lower secondary education or second stage of basic education*
- *Upper secondary education*
- *Post-secondary, non-tertiary education*
- *First stage of tertiary education (not leading directly to an advanced research qualification)*
- *Second stage of tertiary education (leading directly to an advanced research qualification)*
- *Don't know*
- *Refused*

5 *The next questions are about the education of your* [current/most recent] [partner/spouse] *and your parents.*

<Computer aided instrument should filter for respondents without partners/spouse based on question 3.1. If no parent or spouse proceed to 6. Smoking History.>

5.1 Education partner/spouse

What is the highest level of education that your [current/most recent] [partner/spouse] *completed?*

On your screen you will see a number of categories.

Will you please tell me what category applies to your partner?

- *Did not complete primary (compulsory) education*
- *Primary education or first stage of basic education*
- *Lower secondary education or second stage of basic education*
- *Upper secondary education*
- *Post-secondary, non-tertiary education*
- *First stage of tertiary education (not leading directly to an advanced research qualification)*
- *Second stage of tertiary education (leading directly to an advanced research qualification)*
- *Don't know*
- *Refused*

5.2 Education father

What is the highest level of education that your father completed?

On your screen you will see the same categories as before.

Please tell me what category applies to your father.

- *Did not complete primary (compulsory) education*
- *Primary education or first stage of basic education*
- *Lower secondary education or second stage of basic education*
- *Upper secondary education*
- *Post-secondary, non-tertiary education*
- *First stage of tertiary education (not leading directly to an advanced research qualification)*
- *Second stage of tertiary education (leading directly to an advanced research qualification)*
- *Don't know*
- *Refused*

5.3 Education mother

What is the highest level of education that your mother completed?

On your screen you will see the same categories as before.

Please tell me what category applies to your mother.

- *Did not complete primary (compulsory) education*
- *Primary education or first stage of basic education*
- *Lower secondary education or second stage of basic education*
- *Upper secondary education*
- *Post-secondary, non-tertiary education*
- *First stage of tertiary education (not leading directly to an advanced research qualification)*
- *Second stage of tertiary education (leading directly to an advanced research qualification)*
- *Don't know*
- *Refused*

6 Smoking History

Now I would like to ask you a few questions about smoking.

6.1	*Have you ever smoked 100 or more cigarettes in your lifetime?* *<If Yes, proceed to next question.* *<If No, proceed to Closing, End of Interview.>*	▪ *Yes* ▪ *No* ▪ *Don't know* ▪ *Refused*
6.2	*For approximately how many years did you smoke cigarettes?*	_____ *years* ▪ *Don't know* ▪ *Refused*
6.3	*Did you smoke 100 or more cigarettes between* [two years from date of execution of the informed consent and following 12 months]*?*	▪ *Yes* ▪ *No* ▪ *Don't know* ▪ *Refused*
6.4	*Can you remember the name of the brand that you smoked most often during your lifetime, or did you roll your own?* *To help you remember, I would like to show you a selection of the most popular brands smoked.* [Show the brand response cards and record the brand identified.]	▪ *Just one brand (specify)* _____ ▪ *Rolled your own* ▪ *Various brands* ▪ *Don't know* ▪ *Refused*
6.5	*Can you remember how much you smoked on average?* *You can answer how many cigarettes or how many packs per day, per week, per month or per year on average you smoked, which ever you prefer.*	*Amount – cigarettes:* _____ *Amount – packs:* _____ ▪ *Day* ▪ *Week* ▪ *Month* ▪ *Year* ▪ *Don't know* ▪ *Refused*

7 Closing

[End of interview]

(To be handled in interviewer training)

APPENDIX F:
Patient Information/Consent Form

PATIENT INFORMATION AND INFORMED CONSENT FORM

SPONSOR:	THE WEINBERG GROUP LLC 360 Boulevard du Souverain B-1160 Brussels, Belgium
PROJECT TITLE:	Case-Control Study – Disease and risk factors
PATIENT'S NAME:	
PATIENT ID: Note: A patient ID code will be assigned after the informed consent form has been signed.	
INVESTIGATOR'S NAME:	
INVESTIGATOR'S ADDRESS or stamp:	
INVESTIGATOR'S TELEPHONE:	

Dear patient:

Your doctor has invited you to participate in a scientific study being conducted by the research organization THE WEINBERG GROUP LLC. This study is funded by Philip Morris International,

This Patient Information gives you detailed information about this study. After your study doctor has explained the study to you, please take time to read the following information carefully and discuss it with others if you wish (e.g. family members).

Do not hesitate to ask the study doctor to explain any words or information that you do not clearly understand. Before you decide to participate in this study, it is important for you to understand why the study is being conducted and what your involvement will be. If you agree to participate you will be asked to sign this form and will receive a signed copy for your records to take home.

PURPOSE OF THE STUDY:
The purpose of this study is to examine if certain life style choices can influence disease risks and how to minimize these in the future.

DURATION AND SIZE OF THE STUDY:
For this research study, about 2 hours of your time will be required. You do not have to be a smoker or have ever smoked to be able to participate in this study. About 26,000 patients in up to 200 sites in different countries will participate in this study over a period of 36 months.

DESCRIPTION OF THE STUDY:
During this study, you will not receive any study-related medicines and you will not undergo any special medical procedures or treatment in addition to your regular treatment. However, you will be asked to provide information about yourself, your background and family and your health throughout your whole life.

Before continuing, please be assured that all data collected during this study (e.g. your date of birth, interview information, etc.) will be treated completely confidentially. You can find more information on this in the section on data protection and confidentiality.

The questions we will ask you were specially designed for this study. They cover different areas of your life: where you have lived, significant life events, your education, occupation, social and economic status, income, history of tobacco use (if any), diet and alcohol consumption, and medical history. Some personal questions are asked to help you connect and recall different aspects of your life. These questions may be about your partners or children, this information will only used to help you remember other information during the interview, but will not be stored.

In addition to the data being gathered during the interview, your doctor or another trained study team member will document the primary reason for hospital admission from your hospital chart on a case report form designed specifically for the study.

DATA PROTECTION AND CONFIDENTIALITY:
THE WEINBERG GROUP LLC in Belgium will control the collection and processing of all the information collected about you during the study so that it is kept strictly confidential.

The information collected about you, will be held by researchers within THE WEINBERG GROUP LLC and its representatives (Kendle International, PRA International, Axio Research Corporation and the Free University of Amsterdam). To ensure that your personal information is kept confidential, your name will not be included on the questionnaire or any computer data, on the case report forms or on any other records your doctor provides to THE WEINBERG GROUP LLC or its representatives. You will be identified by a unique patient identification code. The identification code is known only to your doctor so that he/she can identify you if it should ever become necessary. Only your study doctor will hold and have access to the confidential list allowing you to be identified. Your doctor is obliged to retain

your study records in strict confidence in accordance with local requirements for at least 10 years after completion of the study.

Data collected will be analyzed in your country, other countries of the European Union (EU), Switzerland and the United States of America. THE WEINBERG GROUP LLC may also share this information with its representatives, ethics committees, government agencies that are overseeing the study. These people and entities may be located in your country, other countries of the EU, Switzerland or the United States. You should be aware that data protection laws vary from country to country, but that everything will be done to protect your personal rights.

Data from all patients documented will be analyzed in a scientific manner and combined results will be submitted for publication in a scientific journal to inform the public about the outcome of the study. Your name will not appear on any report or publication and THE WEINBERG GROUP LLC will ensure that all information that might allow you to be identified, even indirectly, is removed before any information is published.

You have a right to access information collected about you. If you have any questions about the collection and use of this information, or would like to exercise your rights of access, you should ask your study doctor.

BENEFITS:
THERE WILL BE NO MEDICAL BENEFIT TO YOU FROM TAKING PART IN THIS STUDY. However, the results of the study will be of public health interest and might help understanding of the impact of certain risk factors on the occurrence of disease.

VOLUNTARY PARTICIPATION AND WITHDRAWAL:
Taking part in this study is voluntary. If you would prefer not to take part, you do not have to give a reason. Your doctor will not be upset and it will not affect your regular treatment. If you take part, but later change your mind, you can stop your participation in this study at any time by informing your doctor without affecting your present or future care.

If you withdraw from the study prior to or during the interview, the information that has already been collected will be destroyed.

REIMBURSEMENT FOR PARTICIPATION IN THIS STUDY:
You will not be paid for taking part in this study, although a fee of fifty (50) euros will be given to you to cover any travel expenses you may have. There will be no additional payments to you due to your participation in this study

STUDY FUNDING:
THE WEINBERG GROUP LLC is conducting this study with the financial support of Philip Morris International. As Sponsor, THE WEINBERG GROUP LLC will financially compensate the study staff for their work in this study.

PATIENTS' INSURANCE:
While injury is unlikely to occur, THE WEINBERG GROUP LLC will provide insurance for all patients against accidents caused at the study site or traveling to the

study site due to participation in this study. Payment for any medical expenses related to injury directly caused by study related activities will be covered by this insurance. Payment for such things as pain, suffering, and time lost from work is not available. However, it is important that THE WEINBERG GROUP is made aware of any claims on the insurance as soon as possible after the incident or at latest, three (3) months after the date of the interview. Details of the insurance cover are available upon request from your study doctor.

STUDY APPROVAL:
This study has been approved by the ethics committee responsible for your study doctor and the hospital. This committee's role is to ensure that the study has a sound ethical and scientific basis and that your patient and personal rights are adequately protected.

QUESTIONS:
If you think of any additional questions about the study please contact

_____ Tel: _____
Study doctor

Or

_____ Tel: _____
Study coordinator

CONSENT FORM

PROJECT TITLE: Case-Control Study – Disease and risk factors

PLEASE DO NOT SIGN THIS CONSENT FORM IF YOU *DO NOT* WISH TO PARTICIPATE IN THE STUDY OR IF YOUR QUESTIONS HAVE NOT BEEN ANSWERED TO YOUR SATISFACTION.

- I hereby confirm that I have read and understood the information on the information sheet concerning the above mentioned study and that I have had the opportunity to ask questions.
- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.
- I have read and I understand the preceding information describing how information about me will be collected and processed. I consent to the collection and processing of information about me in accordance with national law. I understand that this information will only be used for the purposes described in the preceding Patient Information.
- I authorize the release of information gathered in this study from my medical records and the questionnaire to members of relevant ethics committees, government authorities and authorized representatives and employees of THE WEINBERG GROUP LLC where those individuals are patient to confidentiality obligations in accordance with national law.
- I authorize that my data may be sent to the United States of America for analysis**.**
- I request to receive a copy of the signed consent form for my records.

My signature below indicates that I voluntarily agree to participate in this study, and hereby, give my consent. By signing this form, as a participant in this study, I have not waived any of the legal rights, which I would otherwise have.

Patient's Name (printed)	Signature	Date

Name of Investigator taking consent (printed)	Signature	Date

CONSENT FOR RECORDING OF YOUR INTERVIEW

PROJECT TITLE: Case-Control Study – Disease and risk factors

RECORDING YOUR INTERVIEW:
The interviewer may also make an audio recording of the interview. Researchers within THE WEINBERG GROUP LLC or its representatives will listen to the recordings to evaluate the performance of your interviewer and for internal quality control purposes. The recordings will remain within your country and will not be disclosed to anyone else. They will be destroyed as soon as possible after the interview quality control has been completed.

If you would prefer not to have the interview recorded, it can still take place. The interviewer will switch of the recoding device and confirm that this has been done.

PLEASE DO NOT SIGN THIS CONSENT FORM IF YOU *DO NOT* WISH TO BE RECORDED DURING YOUR INTERVIEW.

- I authorize that my interview can be voice recorded.
- I request to receive a copy of the signed consent form for my records.

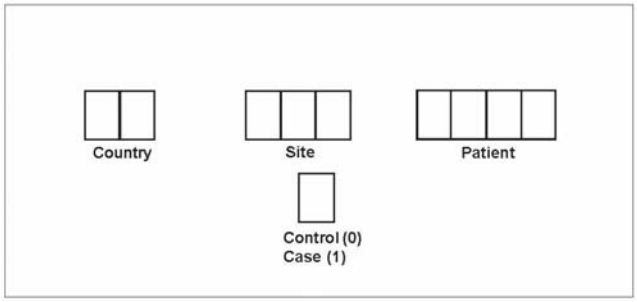
Patient's Name (printed)	Signature	Date

Name of Investigator taking consent (printed)	Signature	Date

APPENDIX G:
Case Report Form (CRF)

Case-Control Study - Tobacco Overview of Risk
C-TOR Study

Case Report Form



SPONSOR:

The Weinberg Group LLC,
360 Boulevard du Souverain
1160 Brussels
Belgium

Top copy to PRA. Bottom copy to be retained at site.

Final: 05-August-2005

ICD 10 Codes for Diagnosis

For Case Subjects

C34.0	Main Bronchus
C34.1	Upper Lobe, bronchus or lung
C34.2	Middle Lobe, bronchus or lung
C34.3	Lower Lobe, bronchus or lung
C34.8	Overlapping lesion or bronchus and lung
C34.9	Bronchus or lung, unspecified

For Control Subjects

C50	Breast Cancer
C61	Prostate Cancer
D05	Breast carcinoma in situ
D24	Benign tumor of breast
D07.5	Carcinoma in situ of prostate
D29.1	Benign tumor of prostate
D50 - D89	Diseases of blood and blood forming organs
E00 - E09	Endocrine, nutritional and metabolic disorders
E15 - E90	Endocrine, nutritional and metabolic disorders
H60 - H95	Diseases of the ear and mastoid process
K35 - K37	Appendicitis
K80	Cholelithiasis
K81	Cholecystitis
L00 - L99	Diseases of the skin and subcutaneous tissue
M00 - M79	Diseases of musculoskeletal system and connective tissue
M83 - M99	Diseases of musculoskeletal system and connective tissue
N00 - N98	Diseases of genitourinary system

C-TOR STUDY	MEDICAL CHART INFORMATION	
Country	Site	Patient

INFORMED CONSENT

DATE INFORMED CONSENT FORM SIGNED: D D M M Y Y Y Y — 2 0 0

DEMOGRAPHIC DATA

Date of Birth: D D M M Y Y Y Y — 1 9

Gender (Please tick): 1 Male 2 Female

Ethnic Origin (Please tick one):
1 Caucasian 4 Oriental
2 Black 5 Other, please specify: _____
3 Asian

DISEASE CHARACTERISTICS

Primary Admission Diagnosis (ICD-10 code for details see previous page): ___ . ___

Date of Diagnosis: D D M M Y Y Y Y

Pathological (e.g. histological, cytological) results available: 1 Yes 2 No — If yes, please specify result: _____

Other diagnostic measures which confirmed diagnosis if applicable:
1 Radiological methods
2 Endoscopic methods
3 Functional tests
4 Laboratory methods:
5 Other, please specify below: _____

INVESTIGATOR'S SIGNATURE _____ 2 0 0

Top copy to PRA. Bottom copy to be retained at site. Final: 05-August-2005

APPENDIX H:
Data Flow