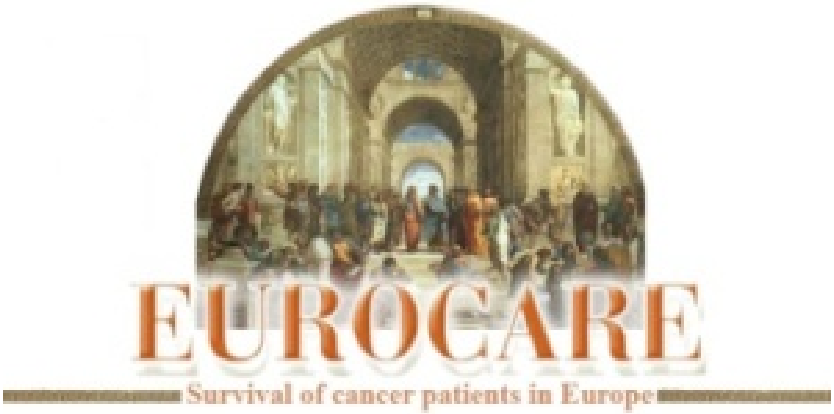

EUROCARE-6

PROTOCOL FOR UPDATING POPULATION-BASED CANCER SURVIVAL IN EUROPE

June 2015

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Sistema Sanitario Regione Lombardia

INDEX

1. INTRODUCTION

EUROCARE is a collaborative research programme on population-based cancer survival in Europe. EUROCARE was set up in 1989 and currently involves 117 population-based cancer registries (CRs) in 31 European countries, providing information on survival for nearly 22 million cancer patients. Most of participating countries are Member States of the European Union.
EUROCARE monitors between country variations and time trends in the survival of cancer patients in Europe, providing key measures to assess the effectiveness of health-care systems in cancer control. EUROCARE's findings have affected the organization of cancer care in several European countries, contributing to the design of national cancer plans and to evaluate their effectiveness. EUROCARE provides scientific evidence to inform health policies, clinicians and citizens and contributes to reduce inequalities and increase standards of cancer care in Europe.

EUROCARE is promoted and coordinated by two Italian research institutes: the Istituto Nazionale Tumori (INT, Milan, IT) and the Istituto Superiore di Sanità (ISS, Rome, IT). The Scientific Direction (SD) of the study is responsible for the study design and project protocols, for data storage, quality control of data, methodological aspects and main data analyses. The SD is supported by the EUROCARE Steering Committee involving experts and representatives from the collaborative network of European cancer registries.

Over the past 25 years EUROCARE has provided systematic, quality controlled and robustly comparable estimates of population-based cancer survival in Europe. The first EUROCARE study included patients diagnosed during 1978-1985 and followed up to 1989[1]. Subsequently the study was extended to include patients diagnosed during 1985-89 (EUROCARE-2), 1990-94 (EUROCARE-3), 1995-2002 (EUROCARE-4), and 2000-2007 (EUROCARE-5)[2,3,4,5,6].
This protocol refers to the EUROCARE-6 study which will analyse survival information up to 2013 in Europe.

1.1. Aims of the EUROCARE-6 project

This protocol incorporates decisions taken by the EUROCARE Steering Committee in Milan, on 29th January 2015.

The EUROCARE-5 round has documented major survival improvements occurring in the first decade of 2000's, as a result of advances in cancer management, as well as persistent international differences, especially between Western and Eastern European countries.

Monitoring changes in cancer patients outcome at the population level remains a major goal of the project. Quality and detail of information collected by the European cancer registries has continuously increased over-time. To address evolving and more specific information needs, survival information should be increasingly provided for clinically relevant cancer entities, e.g. by *morphological sub-type* and by *stage at diagnosis*. Expanding the availability of clinical variables, particularly those relating to stage at diagnosis and summary treatment, is a priority of the EUROCARE-6 study. This will help to improve the comparability and interpretability of survival analyses results.

The EUROCARE-6 call for data will update the EUROCARE database in order to:

- continue monitoring variations in cancer survival by European country/region, age, time and gender, by including up-to-date data from an increasing number of registries;
- extend the use of tumour characteristics that potentially influence treatments and outcome, namely:
  - morphology and sub-site localisation
  - stage at diagnosis;
- study both long-term survival and temporal trends in survival by updating information on life status ascertainment for all cancer patients recorded by cancer registries; for validation and interpretation of survival, incidence may also be analyzed;
- estimate updated cancer prevalence (complete and by disease duration);
- estimate updated incidence, survival and prevalence of rare cancers;
- estimate the proportion of cancer patients who are cured of their disease;
- estimate the number and proportion of avoidable deaths;

1.2. International collaborations: ENCR-JRC call for data protocol and portal

The EUROCARE-6 data call is done in cooperation with the European Network of Cancer Registries (ENCR) and the European Commission Joint Research Center (JRC) - Public Health Policy Support Unit (Ispra,Varese, Italy) - hosting the ENCR secretariat. The Commission Implementing Decision (2011) assigned the JRC's Public Health Policy Support Unit - established within the Institute for Health and Consumer Protection (IHCP) - the task to maintain accurate and comparable EU cancer data. Promoting the harmonization and standardization of cancer information and optimising the collaboration of all stakeholders to provide consistent and up-to-date information have been prioritised by the Commission.

Common variable definitions and up-to-date quality checks procedures have been agreed by ENCR and stakeholders/research projects that analyse cancer registries data (IARC, EUROCARE, CONCORD). Therefore all *core*- and *additional*- variables required by the EUROCARE study are included in the ENCR call for data protocol.

Data files will be transmitted to EUROCARE through a unique portal for data collection implemented by the JRC. By contributing data to the ENCR call 2015 with data flagged for EUROCARE-6, cancer registries adhere to the aims of the present protocol.

1.3. Resources

Resources (personnel, computers and facilities) have been allocated by the INT in Milan and by the ISS in Rome for coordinating the EUROCARE project, checking and analysing data. A dedicated server is available at ISS for data storage. Limited funds for meetings and travel are available at the two Institutes, although a specific budget cannot be stated in advance. Resources for specific, additional initiatives will be sought.

1.4. Confidentiality, security and ethical approval

As in the previous EUROCARE studies, data will be stored individually, but anonymously. Data will be stored in a dedicated server that is not connected to the web, and according to the standard requirements for data security. Data handling conforms with the Confidentiality Guidelines published in 2004 by the International Association of Cancer Registries and IARC and with the relevant European regulation. The ISS regulation on personal data handling published on the Official Journal of Italian Legislative Acts (Gazzetta Ufficiale n.197 of 25/8/2007) complies

with the Italian Personal Data Protection Code (Legislative Decree 196/2003) based on Directives 95/46/EC and 2002/58/EC. The EUROCARE-6 protocol received institutional approval from the ISS Ethical Committee (09/06/2015). The INT Ethical Committe approval will also be made available.

1.5. Data quality checks

Data files will be checked with ad hoc developed procedures. For each tumour record, the validity of each variable, and of combinations of different variables (such as site-morphology or dates sequency), will be checked to detect erratic/unlikely values. Between-records checks will be applied to multiple tumour records with the same patient identification code.

The already existing EUROCARE quality checks procedures will be updated to comply with the recommendations agreed by ENCR, JRC and European research project in a dedicated Working Group on Cancer Data Quality Checks [7].

The records flagged by the data checking process will be sent back to the registries for their revision/correction/confirmation. The JRC portal will be used for these transmissions to- and from-the registries.

1.6. Outcome and publication policy

The main output from EUROCARE-6 will be the publication of survival and prevalence estimates for cancer patients diagnosed and followed up to **31th December 2013**.

The EUROCARE publication policy incorporates data access guidelines approved by the Steering Committee and by the whole EUROCARE Working Group and last updated in September 2004. As in the past edition, the use of the EUROCARE-6 standardised dataset for specific studies will be promoted.

1) The ENCR data will be used within the context of the EUROCARE study by researchers involved directly with the study and as described in the study-approved protocol and in the EUROCARE publication policy. Within this context, the EUROCARE Steering Committee will verify the scientific validity of the proposals and their coherence with the study aims as described in session 1.1. of the EUROCARE-6 protocol.

2) For all other intended usages of the data (for example proposals that fall outside the context of the EUROCARE study, or studies that are validated by the EUROCARE SC but for which the proponents ask for data to be analysed locally) the study proposals explicitly stating how the data will be used (including: study plan, methods to be employed, statistics to be produced and outputs

- publications, websites etc...) will be made available on the ENCR-JRC portal, and cancer registries will be able to sign up to those studies in which they wish to be involved.

2. INCLUSION CRITERIA

2.1. Index tumours

All invasive, primary, malignant neoplasms, except non-melanoma skin cancer, are eligible for inclusion in the EUROCARE-6 study.

In addition, ***in situ*** cancers of **breast, cervix, colon-rectum and skin (melanoma)** are eligible for inclusion. The frequency of *in situ* malignancies for these sites is an indicator of the intensity of screening and early diagnostic activity and can help interpreting international cancer survival differences.

Furthermore, in accordance with the procedures used by many cancer registries, benign, in situ and uncertain behaviour tumours of the **central nervous system** and **urinary bladder** are also eligible for inclusion).

Index tumours occurring in the same person as **multiple primary** tumours, are eligible. Second and higher-order (third, etc...) primary malignancies will be included in cancer survival analyses. Whereby each tumour record will require both a tumour identification code and a patient identification code.

2.2. Period of diagnosis and follow up

Data should be supplied on **all index tumours** diagnosed up to **31 December 2012, however further updates** are welcome, provided that incidence in the territory covered by the registry is complete. Vital status must be updated to **31 December 2013,** or later. Registries are requested to send updated records for **all index tumours**, including those that were included in the EUROCARE-5 study. For tumour records that were submitted for EUROCARE-5, we recommend retaining the **same identification codes**, in order to simplify data quality control procedures.

2.3. Basis of diagnosis and diagnostic classification

Data for all index tumours are requested, including death-certificate-only (DCO) cases, cases discovered incidentally at autopsy, and those lost to follow-up.

Anatomic site, tumour morphology and behaviour must be coded according to the **Third**

Edition of the International Classification of Diseases for Oncology (ICD-O-3), published in 2000 and updated in 2011[8]. Data coded according to previous releases of ICD-O must be converted by the registries with the appropriate existing tools. Please use the ENCR-JRC 2015 Call for Data Registry Questionnaire to provide information on the ICDO revisions.

3. GUIDELINES FOR DATA SUBMISSION

Three data files are expected from each participating registry including respectively: data on diagnosis and follow up (patients' survival file), data on annual life tables (life tables file) and number of resident persons (population file) in the territory covered by the registry. Registries are also requested to provide standardized information on the data collection process by filling in the ENCR-JRC 2015 Call for Data Questionnaire.

3.1. Deadline for data transmission

The deadline for transmitting data through the JRC-ENCR portal is **September 4th 2015.**

3.2. Patients'survival data

For each index tumour the following **core** and **additional** variables are required.

The full description of the variable list and coding is included in the Submission Guidelines of the ENCR-JRC 2015 Call for data.

1. Check flag (1_Flag) (core variable)
2. Patient identification code (2_Patient_ID) (core variable)
3. Tumour identification (3_Tumour_ID) (core variable)
4. Day of birth (4_Day_DoB) (core variable)
5. Month of birth (5_Month_DoB) (core variable)
6. Year of birth (6_Year_DoB) (core variable)
7. Sex (7_Sex) (core variable)
8. Day of incidence (8_Day_DoI) (core variable)
9. Month of incidence (9_Month_DoI) (core variable)
10. Year of incidence (10_Year_DoI) (core variable)
11. Age (11_Age) (core variable)
12. Basis of diagnosis (12_BoD) (core variable)
13. Topography (13_Topo) (core variable)

14. Morphology (14_Morpho) (core variable)
15. Behaviour (15_Beh) (core variable)
16. Grade (16_Grade) (core variable)
17. Incidental finding of cancer at autopsy (17_Autopsy) (core variable for survival studies)
18. Last known vital status (18_Vital_status) (core variable for survival studies)
19. Day of last known vital status (19_Day_FU) (core variable for survival studies)
20. Month of last known vital status (20_Month_FU) (core variable for survival studies)
21. Year of the last known vital status (21_Year_FU) (core variable for survival studies)
22. Duration of survival in days (22_Survival) (conditional core variable for survival studies)
23. Laterality of paired organs (23_Laterality) (additional variable)
24. Day of case registration (24_Day_DoR) (additional variable)
25. Month of case registration (25_Month_DoR) (additional variable)
26. Year of case registration (26_Year_DoR) (additional variable)
27. Official underlying cause of death (27_Cause_death) (additional variable)
28. ICD edition for cause of death (_ICD_edition) (additional variable)
29. TNM prefix (29_TNM_prefix) (core variable)
30. TNM stage, pathological primary site T (30_pT) (core variable)
31. TNM stage, pathological lymph nodes N (31_pN) (core variable)
32. TNM stage, pathological metastases M (32_pM) (core variable)
33. TNM stage, clinical primary site T (33_cT) (core variable)
34. TNM stage, clinical lymph nodes N (34_cN) (core variable)
35. TNM stage, clinical metastases M (35_cM) (core variable)
36. TNM stage grouping (36_Stage) (core variable)
37. TNM edition (37_TNM_edition) (core variable)
38. Condensed TNM T (38_Cond_T) (core variable)
39. Condensed TNM, N (39_Cond_N) (core variable)
40. Condensed TNM, M (40_Cond_M) (core variable)
41. Dukes' stage (41_Dukes) (additional variable)
42. FIGO stage (42_FIGO) (additional variable)
43. ANN ARBOR stage (43_AArbor) (additional variable) (for Lymphomas only)
44. GLEASON grading (44_Gleason) (additional variable) (for prostate cancer only)
45. BRESLOW thickness (45_Breslow) (additional variable)

46. Summary extent of disease (46_EoD) (core variable)
47. Tumour size in millimetres (mm) (47_Tsize) (additional variable)
48. Number of nodes examined (48_N_exam_nodes) (additional variable)
49. Number of metastatic nodes (49_N_met_nodes) (additional variable)
50. Sentinel nodes (50_Sent_nodes) (additional variable)
51. Metastases in sentinel node (51_Met_sent_nodes) (additional variable)
52. C factor (52_Cfactor) (additional variable)
53. Surgery (53_Surgery) (additional variable)
54. Systemic anti-cancer therapy, including chemotherapy, targeted, immunotherapy and hormone therapy (54_Systemic_th) (additional variable)
55. Radiotherapy (55_Radiotherapy) (additional variable)
56. Bone marrow transplantation (56_BMtransp) (additional variable)

3.3 Life tables

Life tables, i.e. the background mortality in the general population of the administrative territory covered by the cancer registry, must be provided by registries participating in survival studies.

Registries that participated in previous EUROCARE rounds are requested to update follow-up at the most recent available year (up to 2013, or later). Registries participating in EUROCARE for the first time should send life tables covering their entire period of incidence (up to 2012 at least) and follow-up (up to 2013).

All-causes mortality rates in the general population, by sex, age and calendar year, should be provided to 6 decimal places or an equivalent number of significant figures (e.g. 0.012345 for a rate of 1,234.5 per 100,000).

Since mortality rates are highly dependent on age, values should be preferably given in one-year age classes (from 0 to 99 or more). If this is not possible, age should be grouped by no more than five years: in this case, please specify how the life tables were smoothed.

It is essential to have accurate mortality data for the elderly to accurately estimate relative survival in this age group. The oldest age class can be open (e.g. 90 years and over), but the low boundary of the oldest age class should not be less than 85 years.

For national cancer registries, life tables can be provided by administrative region (if there are significant differences in all causes mortality by region within the country). In this case the administrative region must be also provided for each patient record in the file of cancer cases.

Please document the source of demographic data and provide the **name and e-mail address** of a **reference person** to contact for more detailed information on demographic and mortality data in the general population, in the event of queries.

For further details see Submission Guidelines of the ENCR-JRC 2015 Call for data, available on the ENCR website.

3.4. Population data

Data on the population of the area covered by each registry are required for computing prevalence and for checking data completeness. Registries should supply tables with the number of inhabitants in the registry area. Data from official censuses or inter-census estimates provided by Vital Statistics Departments or other official sources should be used for this.

Population data must be supplied for each calendar year by age (5-year age classes) and sex for the entire time span of incidence data.

For further details see Submission Guidelines of the ENCR-JRC 2015 Call for data.

4. REFERENCES

1. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Estève J, eds. Survival of cancer patients in Europe: the EUROCARE study (IARC Scientific Publications No. 132). Lyon: International Agency for Research on Cancer; 1995
2. Berrino F, Capocaccia R, Estève J, Gatta G, Hakulinen T, Micheli M, Sant M, Verdecchia A, eds. Survival of cancer patients in Europe: the EUROCARE-2 study (IARC Scientific Publications No. 151). Lyon: International Agency for Research on Cancer; 1999
3. Berrino F, Capocaccia R, Coleman MP, Estève J, Gatta G, Hakulinen T, Micheli A, Sant M, Verdecchia A, eds. EUROCARE-3: the survival of cancer patients diagnosed in Europe during 1990-94. Ann Oncol 2003; 14 (Suppl. 5): pp1-155
4. Capocaccia R, Gavin A, Hakulinen T, Lutz JM, Sant M (eds.). Survival of cancer patients in Europe, 1995-2002. The EUROCARE-4 Study. Eur J Cancer 2009; 45
5. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. Lancet Oncol 2014;15(1):23-34
6. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5-a population-based study. Lancet Oncol 2014;15(1):35-47
7. http://publications.jrc.ec.europa.eu/repository/handle/JRC93456
8. International Agency for Research on Cancer and World Health Organization. 2011 Updates to ICD-O-3: http://www.who.int/classifications/icd/updates/icd03updates/en/index.html