| Ministero della Salute<br>Direzione Generale della Ricerca Sanitaria e Biomedica e della Vigilanza sugli Enti<br>BANDO 2016 PROGETTO COMPLETO | **Project Title:**<br>Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation |
|---|---|
| **Project Code:** RF-2016-02363990 | **Principal Investigator:** Abraha Iosief |
| **Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4 | **Applicant Institution:** Umbria |

# Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

**Project Classification IRG:** Healthcare Delivery and Methodologies

**Project Classification SS:** Biostatistical Methods and Research Design - BMRD

**Project Keyword 1:** Data analysis and modeling: development of statistical theory, analytic methods and models, computational tools and algorithms for the analysis and interpretation of data from clinical studies, randomized trials, epidemiological studies, human genetic association studies, environmental studies, and complex surveys; methods to handle data features and anomalies such as correlation, clustering, missing and skewed data; risk prediction and forecasting methods; causal modeling; high dimensional data methods

**Project Keyword 2:** validity; confounding; propensity score; instrumental variable; treatment selection bias

**Project Keyword 3:** administrative healthcare database; ICD-9 code

**Project Request:** **Animals:** ☐ **Humans:** ☐ **Clinical trial:** ☐

**The object/s of this application is/are under patent copyright Y/N:** ☐

**Operative Units / WP**

| | INSTITUTION | Department/Division/Lavoratory | Role in the project |
|---|---|---|---|
| 1 | Umbria | Office of Health Planning | Principal Investigator Unit. Coordination of the overall project, protocol development, validation of icd-9 codes, medical chart review, data analyses, statistical analysis, writing reports |
| 2 | Marche | Office of Health Planning | In conjunction with Umbria unit: protocol development, validation of icd-9 codes, medical chart review, data analyses, statistical analysis, writing reports |
| 3 | Marche | - | - |

**Investigators, Institution and Role in the Project**

| | Co-PI | Key Personnel | Institution/Org./Pos. | Role in the project | Birth Date |
|---|---|---|---|---|---|
| 1 | | Di Furia Lucia | Marche | MD. She will lead the Marche team for the conduct of the project. | 24/12/1957 |
| 2 | | Spazzafumo Liana | Marche | Biostatistician. She will plan and conduct statistical analyses within the data from the Marche regional administrative database. | 17/03/1961 |
| 3 | X | Eusebi Paolo | Umbria | Biostatistician. He will plan and conduct statistical analyses within the data from the Umbria regional administrative database. He will also assist the PI in the overall handling of the project. | 08/05/1976 |
| 4 | | Orso Massimiliano | Umbria | MSc. He has experience in data abstraction for validation purposes. He will contribute in developing abstraction forms, data abstraction and writing reports. | 30/10/1977 |

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## Overall Summary

Administrative healthcare databases are increasingly recognized as valuable resources for disease surveillance and research. Hence, it is mandatory to validate the diagnosis codes contained in these databases and to control for selection bias and confounding. Despite the widespread availability of administrative databases in Italy, their use is limited due to a lack of systematic validation of ICD-9 codes for relevant diseases. The main objectives of this project are: to validate diagnosis codes for cardiovascular conditions (myocardial infarction, heart failure, atrial fibrillation) and related outcomes (stroke and gastrointestinal hemorrhage) from two Regional Administrative Databases (Umbria and Marche, covering 2.4 M residents); to search for an appropriate statistical model to control selection bias and confounding; and to find suitable ways to manage missing data. The findings of this proposal will provide real-time disease surveillance, effectiveness and safety evaluations.

## Background / State of Art

Since administrative healthcare databases store information on drugs and health outcomes for large populations in a timely fashion, they are increasingly being recognized as a preferred data source for comparative effectiveness research and disease surveillance [1]. Risks for their use as a reliable source of data is a lack of validation of diagnosis codes and the presence of confounding factors. Thus, validating these codes is the first step that must be undertaken. Employing a validation process with multiple diagnosis codes avoids the time-consuming re-abstracting of medical charts and allows assessments to be performed in a short period of time.
To control for confounding and selection bias, recent developments, such as the concept of proxy variables, using high dimensional propensity scores, and provider variation exploitation, using instrumental variable analysis, have been proposed and applied successfully[2, 3].
In Italy, despite the widespread presence of administrative databases, recent evidence demonstrates that few of these databases have been validated [4]. Hence, an extensive process of validation is warranted.
We propose the validation of diagnosis codes for relevant cardiovascular diseases that are associated with significant morbidity, mortality, physical disability, reduced quality-of-life, and economic effects [5].

## Hyphotesis and Specific AIMS

**Hyphotesis and Significance:**
Internal validity of healthcare databases is essential if they are to be used as reliable sources of data. Misclassification of diagnostic codes, selection bias, confounding and missing data are elements that can affect the validity of healthcare databases[6]. Therefore, validating ICD-9 codes, testing appropriate models that control for confounding factors and handle missing data will lead to robust data for disease surveillance and comparative effectiveness research[3, 7].
Since cardiovascular conditions are very common and are associated with high rates of morbidity and mortality, and significant economic effects, we propose validating ICD-9 diagnosis codes for the following medical conditions: myocardial infarction, heart failure and atrial fibrillation (AF), together with two related medical outcomes (stroke as a consequence of untreated AF and gastrointestinal hemorrhage as a side effect of anticoagulation treatment). Moreover, we plan to test methods to control for confounding factors and to handle missing data in populations with cardiovascular disease identified from administrative databases from two Italian regions (Umbria and Marche).

**Preliminary Data:**
A recent update of a systematic review[4] demonstrated that the issue of validity of administrative databases need to be adequately addressed (Tab 1).

Average rates of hospitalizations between 2010 and 2015 average for the outcomes of interest are displayed in Figure 1. Rates are similar in terms of myocardial infarction, heart failure, stroke. While Umbria region showed higher rates for AF, Marche region showed higher rates for heart failure (Fig 1).
Preliminary data shows that 2/3 of incident subjects with AF in Umbria (2005) region did not receive any anticoagulation or antiplatelet therapy during the subsequent 5 years. The incidence of subsequent events for treated and untreated patients are displayed in Fig 2. Compliance, the position of the diagnosis, treatment selection bias need to be accounted.

**Specific Aim 1:**

To validate ICD-9 codes for: (i) myocardial infarction (code: 410.x ); (ii) atrial fibrillation (code: 427.31); and (iii) heart failure (code: 428). According to our preliminary assessment, three other medical conditions were related to at least one of the aforementioned diseases: (a) ischemic stroke (codes: 433.x1, 434 (excluding 434.x0); (b) hemorrhagic stroke (codes: 436.x for, 430.x and 431.x); and (c) gastrointestinal bleeding (codes: 531, 532, 533, 534, and 578).

**Specific Aim 2:**

To compare the relative yield of analytical methods to control for the effect of selection bias and confounding occurring in: (i) observational evaluations of efficacy; (ii) safety assessment; and (iii) risk factor estimation. The following methods will be applied: multivariable model risk adjustment, propensity score risk adjustment, propensity-based matching, and instrumental variable analysis. The data obtained will also be compared with information on this topic from the published medical literature.

**Specific Aim 3:**

To assess the relative efficiency of multiple imputation (MI) [Carpenter and Kenward 2012] approaches for handling missing data in large complex databases under Missing At Random assumption (MAR). Investigated scenarios will involve mixed types of variables (categorical/continuous) at different levels of the model (outcomes and/or predictors). Investigated approaches will be: complete-case analysis; MI based on multivariate normal distribution with rounding the non-integer imputed values to the nearest feasible integer for categorical variables; MI based on chained equations[8]; MI based on the standard general location model [9]; a novel MI approach based on mixture models [10] (Tab. 2).

**Experimental Design Aim 1:**

A cross-sectional diagnostic accuracy study design. The source population will be permanent residents, aged 18 years and older, in the Umbria and Marche regions. Residents with hospital admissions outside these two regions will be excluded. For each target disease (e.g., myocardial infarction), a random sample of patients will be obtained from each healthcare database using the corresponding ICD-9 code (i.e., 410.x). Subsequently, the corresponding medical charts of the randomly selected cases will be obtained from hospitals for review. Paired trained chart abstractors will abstract data independently. Case ascertainment will be performed by medical doctors in the field using internationally recognized criteria to validate each ICD-9 code diagnosis. We will validate two different samples for incident (important for surveillance of adverse effects) and prevalent (important to calculate disease burden) outcomes.

**Experimental Design Aim 2:**

We will apply all 4 statistical models, and measure relative outcomes, to two cohorts of patients identified in the two regional databases:
(a) Adults with AF, discharged between 2008 and 2010 and followed up to 2015. Subjects will be stratified according to treatment received (classical oral anticoagulant agents (e.g., warfarin), new oral anticoagulants (e.g., dabigatran), aspirin alone, no treatment. Further stratification will be performed with respect to compliance to treatment (treatment covering at

least 80% of the period of observation, between 80% and 60%, and less than 60%).
In this cohort, the effect of these treatments will be evaluated on hard efficacy end-points (non-fatal ischemic stroke, and mortality).
In this cohort, we will also assess safety and safety outcomes of these treatments (hemorrhagic stroke and gastrointestinal hemorrhage).
(b) Adults with acute myocardial infarction, enrolled between 2008 and 2010 and followed up to 2015. Prognostic factors that predict long-term outcomes (re-hospitalization for acute myocardial infarction and heart failure, and mortality) will be examined. Subjects will be stratified according to STEMI vs non-STEMI, and invasive approach (coronarography, eventually followed by PTCA or by-pass) vs conservative strategy. In this cohort, we will also assess prognostic risk factor estimation.

**Experimental Design Aim 3:**
We will apply the 5 proposed statistical models to the cohorts indicated in Aim 2. We will compare computational time and impact on the final estimates and their confidence intervals.

**Picture to support preliminary data:**
Picture.Final.Umbria-Marche.pdf

**Metodologies and statistical analyses:**
Aim 1. For each medical diagnosis, we will identify patients, discharged across a period of three years, in the two regional administrative databases. A random number generator will be used to select a subset of patients for our reference standard abstraction. A standardized form, specific to each disease target, will be produced to record demographic, clinical, laboratory and instrumental (ECG) data. Clinically trained chart reviewers will examine the medical charts and fill in the specific form. Before proceeding to full medical chart abstracting, agreement between pairs of reviewers will be assessed for a limited number of charts.
Anonymous code of the patient, date of birth, gender, dates of hospital admission and discharge, any diagnostic procedure(s) that contributed to diagnose the disease, any pharmacological or surgical interventions that were provided will be obtained from the medical chart.
The number of medical charts estimated to be required was based on a PPV with a 5% margin of error. With a 95% confidence level, a sample size of 62 for each ICD-9 code is needed to achieve a 5% margin of error for the estimate of sensitivity, specificity and predicted values.

Validation criteria will be based on standardized internationally recognized criteria. For example, for myocardial infarction, the ICD-9 code 410.x will be considered valid when there is evidence of at least two of the following conditions [11: (i) cardiac symptoms; (ii) enzyme alterations (including troponin, LDH, ect.); or electrocardiogram alteration. For heart failure, the ICD-9 code 428.x will be considered valid when there is evidence of at least two of the following conditions (as defined by European guidelines[12]): (i) prior clinical history, clinical findings or ECG alterations; (ii) elevated levels of plasma natriuretic peptide; or (iii) ventricular insufficiency documented with echocardiography.
The diagnosis will be classified as definite or indeterminate. Reports will be developed using the STARD criteria[13].
Statistical analysis - Sensitivity, specificity and positive and negative predictive values will be calculated separately for each code and for each region.

Aim 2. The conventional multivariable model risk adjustment, the propensity score risk adjustment[14], the propensity-based matching[15], and the instrumental variable analysis[16] will be applied.

Statistical approaches will be tested in both cohorts to determine computational time and impact on final estimates and relative uncertainty measures.
Aim 3. Performances of MI approaches will be tested with simulated scenarios and real-world data using the cohorts reported in Aim 2. Simulations will be generated under a number of scenarios accounting for different patterns of missing data and different characteristics of variables. The scenarios for missing data will account for different items: position of the diagnosis (primary position, secondary position, any position), incidence of disease, prevalence of disease and average proportion of missing data (from 5% to 25%). MI approaches will be compared in simulations by means of computational time, bias, mean squared error and coverage probability. MI techniques will be tested in analyzed cohorts to determine computational time and impact on final estimates and relative uncertainty measures.

**Expected outcomes:**

In general, Italian administrative databases have successfully addressed important questions in post-marketing surveillance based on chart abstraction[17]. We expect to gain an acceptable degree of accuracy especially in terms of sensitivity and positive predictive values of the diagnosis codes of interest. This will allow systematic and timely disease surveillance.
The statistical methods proposed to address the issue of selection bias have been used within large observational datasets with the aim of mitigating the bias introduced by measured and unmeasured confounding factors that can affect non-experimental data. While propensity scores and propensity-based matching are most suited to answer specific clinical questions for a specific patient, instrumental analysis is most suited to answer policy-relevant questions [19]. We expect that the results from the application of the 4 statistical models will provide insights in the type of questions that each type of model will be be able answer and tosuggest future application.
Missing data are frequently encountered in large datasets and have the potential of leading to biased estimates of treatment effects, but this issue is still under investigated. Besides the case of sample selection, a realistic hypothesis is to assume that the missing data are MAR, that is, the probability that an observation is missing may depend on observed data, but not on other missing values or non-observed variables. A rigorous assessment of the performance of different statistical approaches is needed in order to have unbiased estimates leading to more informed healthcare decisions. Our investigation will inform future studies both in different diseases and different databases.

**Risk analysis, possible problems and solutions:**

The overall research is based on healthcare databases in which anonymity of the patients is assured. Efforts will be made to preserve anonymity when medical charts are being examined.
Since previous research based on consulting medical charts has been performed using the Umbria database [17] we expect to obtain an acceptable predictive value for each ICD-9 code. Where inadequate levels of validity occur, algorithms reported in the medical literature will be applied to enhance accuracy. In case this option fails, the results will be analyzed to identify potential causes of misclassification and solutions proposed for future validation processes.

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# Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Significance and Innovation

This proposal will be the first validation process of ICD-9 codes for the most prevalent cardiovascular diseases to be performed in Italy and involving two Regional Health Authorities, with a combined population of 2.4 million residents. The project will also provide an appropriate framework for conducting comparative effectiveness research, disease and medication surveillance and epidemiologic studies on an unprecedented scale and importantly, the study can suggest the best methodological approach for the type of analysis to be made. The two databases provide a chance for networking offering an external validity that is greater than that of randomized trials and thus will help to answer a wide spectrum of research questions in cardiovascular disease, contribute to the improvement of the quality of health service delivery, and construct a framework for the future validation of disease codes in other fields.

## Description of the complementary and sinergy research team

To ensure quality, an External Advisory Board (EAB), composed of internationally accredited professionals, will be involved: Frank de Vries (Maastricht University); Daniel Prieto-Alhambra, Spanish (SIDIAP); Tjeerd van Staa (Clinical Practice Research Datalink).
In aim 1, both Units, from the Umbria and Marche Regions, will benefit from the contribution of the Institute of Cardiology of the University Hospital of Perugia lead by Prof. Giuseppe Ambrosio (H index of 49) for case ascertainment, during and after data abstraction.
Professionals from the Information Technology departments of the two Units will be involved in randomly selecting the patients with the diagnoses of interest. Paolo Eusebi will lead the data management and statistical analysis for the Umbria Region, with the involvement of Paola Casucci, and the data managers Marcello De Giorgi and David Franchini. Dr. Alessandro Montedori from the Umbria Regione (H-index=8, with experience in validation processes) will provide methodological support during the process of validation and selection of the two cohorts of patients.
Lucia di Furia will supervise the work in Unit 2. Dr. Liana Spazzafumo will lead the data management and statistical analysis within the Marche Region. Methodological and analytical issues will be shared among the two groups in order to take advantage of the expertise of each team member. Analyses will be assessed with the involvement of both Units and results will be interpreted together.

## Training and tutorial activities

To fill the gaps in research methodology, all the teams, together with new collaborators, will take courses in pharmacoepidemiology and research methodology. Residential courses and workshops, mainly directed towards junior researchers, will be organized. The content will regard the management and analysis of administrative, and other healthcare databases, for research purposes. In general, methods used for observational studies, including issues regarding validity and reliability of databases, will be reviewed. Special courses will also be conducted, concerning statistical methods for multivariable model risk adjustment, propensity score risk adjustment, propensity-based matching and instrumental variable analysis.
Workshops will be provided to researchers involved in data abstraction of medical charts. During data abstraction, tutorial activities will be provided by senior cardiologists. Members of the EAB will be involved in the training.

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**Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata**

## Bibliography

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2. Stukel Analysis of observational studies in the presence of treatment selection bias. JAMA, 2007 297 278
3. Schneeweiss, Methods in pharmacoepidemiology Pharmacoepidemiol Drug Saf 2005 14 453.
4. Abraha, The current state of validation of administrative healthcare databases in Italy. International Journal of Statistics in Medical Research 2014 3 309.
5. Nichols Cardiovascular disease in Europe. Eur Heart J 2013 34 3028
6. West Validity of Pharmacoepidemiologic Drug and Diagnosis Data. Pharmacoepidemiology. 2007 Wiley. 709-765.
7. Faris Multiple imputation versus data enhancement for dealing with missing data. JCE 2002. 55 184
8. van Buuren Multiple imputation of discrete and continuous data. Stat Methods Med Res 2007. 16 219-42.
9. Olkin Multivariate Correlation Models. Ann Math Statist 1961 448
10. Eusebi Mixture models for multiple imputation of missing data in longitudinal settings. IBS Austro-Swiss-Italian Italy 2015.
11. McCormick Validity of myocardial infarction diagnoses in administrative databases PLoS One 2014. 9 e92286.
12. Ponikowski 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure:. Eur J Heart Fail 2016.
13. Bossuyt Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD Initiative. Ann Intern Med 2003. 138 40
14. D'Agostino Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998. 17 2265
15. Rosenbaum Constructing a Control Group Using Multivariate Matched Sampling Methods. The American Statistician 1985. 39 33
16. Newhouse Econometrics in outcomes research: the use of instrumental variables. Annu Rev Public Health 1998. 19 17
17. Traversa Cohort study of hepatotoxicity associated with nimesulide. BMJ 2003. 327 18
18. Harris Understanding instrumental variables estimates of treatment effects. Health Serv Res 1998. 33 1337

## Timeline / Deliverables / Payable Milestones

The overall estimated study duration is 36 months. The work will begin with aim 1, starting with a case definition for the reference standards, drafting a standardized format (medical chart abstraction) of each diagnostic code and the training of chart reviewers, as well as the testing of their level of agreement. The intention is to complete the chart abstraction for all the diagnoses within the second year. At 30 months accuracy data analysis will be completed and final reports will be submitted to journals.
Aim 2 will start in the second semester of the second year during which the two cohorts will be identified.
Aim 3 will start at 18th month.
By the end of the third year all the tasks (of all aims) will be accomplished and the results will be drawn together for the drafting of the final papers.

## Milestones 18 month

A critical task in the validation process will be the examination of the selected medical charts in order to extract data regarding the chosen ICD-9 diagnosis codes. We estimate a good result to be the examination of at least 60% of the entire

random sample of medical charts within 18 months from the project start-up.
Identification of two cohorts of patients from the two regional databases and publication of the study design (observational study protocol).

## Milestones 36 month

At the 36 month milestone, all the aims will be completed.
A report of the results regarding the validation of the ICD-9 codes will be provided (cross-sectional diagnostic accuracy studies).
A report of the outcome of the application of the statistical models will be provided.
Several final manuscript drafts will be completed.

## Gantt chart

GantTT_Marche-Umbria_Final.pdf

## Equipment and resources available

Both Regional Health Authorities have access to their own healthcare information systems that maintain large administrative databases and routinely monitor coding errors, assess healthcare utilization patterns, monitor healthcare outcomes, and produce reports on drug and hospital admissions for audits, surveys and researches purposes. The two Units have qualified professional and administrative personnel. The professionals include medical doctors (with clinical, epidemiological and public health backgrounds), pharmacists, statisticians, economists and data management experts. In addition, both Units have adequate information technology infrastructures including computers with the most updated software (SAS and STATA) to manage big data, projectors, printers and photocopy machines. The Department of Cardiology (Head Prof. Giuseppe Ambrosio) has qualified professional personnel with extensive skills, experience and equipment in cardiology.

## Translational relevance and impact for the National Health System (SSN)

The immediate implication of the project will be the availability of the real figures regarding cardiovascular diseases (e.g., the burden of stroke due to untreated AF) for the Italian NHS. Consequently, the latter will be able to monitor and put in place appropriate measures to reduce negative outcomes. In addition, these validated databases will be very useful to characterize patients who have long-term compliance with anticoagulants, to identify patients who are likely to be candidates for new or old oral anticoagulants, and to perform further investigations on these new compounds. Similar assessments can be performed for sacubitril, a new promising drug for heart failure, that is being introduced into the Italian market. In terms of long-term implications, these validated databases can provide real-time assessment of safety issues that may arise on newly released (or old) compounds, in terms of cardiovascular outcomes, as well as stroke and gastrointestinal hemorrhage.

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## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## PRINCIPAL INVESTIGATOR PROFILE


| Name | | |
|---|---|---|
| Abraha Iosief | Institution | Umbria |
| | Department/Unit | Health Planning Office, Regional Health Authority of Umbria |
| | Position Title | Collaborator |

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| Education/Training - Institution and Location | Degree | Year(s) | Field of study |
|---|---|---|---|
| Faculty of Medicine, University of Perugia, Perugia | Degree in Medicine (MD) | 6 | Medicine and Surgery |
| Postgraduate School of Internal Medicine, University of Perugia, Perugia | Post-graduate Diploma in Internal Medicine | 5 | Specialty in Internal Medicine. The Department of Internal Medicine had a large experience in the management of oncohaematological diseases, management for neutropenic patients, auto-immune diseases, and infectious diseases. |
| National Institute of Health (Istituto Superiore di Sanità), Rome, Italy. | Course (1 week) | 0 | Pharmacoepidemiology, Disease modelling, Study designs, Administrative Healthcare Databases; Drug compliance, Adverse Drug Reactions |
| University of Milan, Milan, Italy | Master in Systematic Review Methodology. | 1 | Systematic review, metaanalysis, search strategy in medical literature, quality assessment of randomized trials and observational studies, random and fixed effect, heterogeneity, publication bias. |
| University of Modena and Reggio Emilia, Modena, Italy | Master in Evidence-Based Medicine and Methodology of Research in Healthcare (achieved in 2006). | 2 | Evidence-based medicine, the concept of PICO, risk of bias; study designs: randomized and observational studies, diagnostic studies, cost-effectivenes studies; principles of statistics; measures of association; systematic reviews and meta-analysis. |

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| Education/Training - Institution and Location | Degree | Year(s) | Field of study |
|---|---|---|---|
| McMaster University - Hamilaton, ON, Canada | How to Teach Evidence-Based Clinical Practice (achieved in 2009; duration 1 week) | 0 | Evidence-based clinical practice (EBCP) is an approach to health-care practice that explicitly acknowledges the evidence that bears on each patient management decision, the strength of that evidence, the benefits and risk of alternative management strategies, and the role of patients' values and preferences in trading off those benefits and risks. The course is designed for clinician educators interested in enhancing their skills for teaching the principles of evidence-based practice to others. |
| Universita' La Cattolica, Rome, Italy | Course in statistics (achieved in 2007; duration 2 weeks) | 0 | Regression Analysis by Prof. S. Lemeshow; Survival Analysis by Prof. Hosmer. |
| University of Amsterdam, Amsterdam, Netherlands | Course in Diagnostic systematic review (achieved 2008; duration 1 week) | 0 | Developing a Cochrane Diagnostic Test Accuracy Review. Organized by the Cochrane diagnostic study group (1 week). The PI developed and published a Cochrane diagnostic protocol: Abraha, (2013) "Ultrasonography for endoleak detection after endoluminal abdominal aortic aneurysm repair." Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD010296. Final review submitted for publication |

## Personal Statement

My expertise is in methodological field. I have recently addressed the bias related to deviation from intention-to-treat in randomized trials. I have also experience in drug reviews and compliance as well as pharmacoepidemiology using administrative databases. I am currently involved in the validation process of ICD-9 codes of oncological diseases. The project aims to assess the validity of two Regional Administrative Databases (Marche and Umbria). My responsibility will be

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handle the overall project, coordinate the work between the regional Institutions.

**Positions and Honors**

| Institution | Division / Research group | Location | Position | From year | To year |
|---|---|---|---|---|---|
| Regional Health Authority of Umbria | Office of Health Planning | Perugia, Italy | Consultant on Pharmacovigilance, Pharmacoepidemiology, Drug Utilization Review, Systematic Reviews production, Guideline Development | 2002 | 2016 |
| Italian National Research Center on Aging (INRCA) | Geriatrics and Geriatric Emergency Care | Ancona, Italy | Consultant for a European Union funded research Project SENATOR (Software ENgine for the Assessment & Optimization of drug and non-drug Therapy in Older persons; http://www.senator-project.eu/) Meta-analysis and Guideline recommendation based on the GRADE approach on Non-Pharmacological Interventions to treat and prevent 15 geriatric condition. | 2013 | 2014 |
| National Agency for the Regional Health Services (Agenzia Nazionale per i Servizi Sanitari, AGENAS | Department of Innovation and Health Technology Assessment | Rome, Italy | Consultant (production of systematic reviews and HTA reports) | 2012 | 2016 |
| ASUR - Marche, Area Vasta 1 | Continuità assistenziale (ex Guardia Medica) | Urbino (PU) | General Practitioner/physician (part-time) | 2004 | 2013 |

## Grant, Awards and Honors

**Official H index:** 11.0

**Source:** Scopus **Scopus Author Id:** 55944056600

**ORCID ID:** orcid.org/0000-0002-5440-775X **RESEARCH ID:** -

**Awards and Honors:**

Grant from the Ministry of Health. Project title: Impact of Modified Intention to Treat Reporting on Treatment Effect in Metaanalyses: A Meta-Epidemiological Study. Total budget: 180,000 euros. RF-2009-1549561
Member of the Ethics Committee of University of Camerino (2007-2009)
Member of the Regional Ethics Committee of Umbria (2004-2015).
Reviewer for: BMJ, BMJ Open, Plos One, Journal of Clinical Epidemiology, BMC Medical Research Methodology

**Other CV Informations:**

The PI has both clinical and biomedical methodology research expertise (EBM, Cochrane meta-analysis, pharmacoepidemiology and HTA; use of SAS and STATA). Main methodologist of an EU funded project (http://www.senator-project.eu/ WP2). Consultant to the National Agency (Agenas) for the development of HTA reports. He

| | |
|---|---|
| | **Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation |
| **Project Code:** RF-2016-02363990 | **Principal Investigator:** Abraha Iosief |
| **Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4 | **Applicant Institution:** Umbria |

**Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata**

successfully investigated the issue deviation of intention-to-treat in a meta-epidemiological analysis. He is working in the assessment of disease case definition and validation for several oncological diseases in a the Umbria administrative database (BMJ Open 2016).

**Project Title:**
Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

# Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Selected peer-reviewed publications of the PI

**Valid for PI minimum expertise level**

| Title | Publication / Journal | Pag | Vol | Year | DOI | PMID | IF | Cit. | P.* |
|---|---|---|---|---|---|---|---|---|---|
| Validity of ICD-9-CM codes for breast, lung and colorectal cancers in three Italian administrative healthcare databases: a diagnostic accuracy study protocol. | BMJ Open | e010547 | 6 | 2016 | 10.1136/bmjopen-2015-010547 | 27016247 | 2.562 | 1 | F |
| The current state of validation of administrative healthcare databases in Italy: a systematic review | International Journal of Statistics in Medical Research | e010547 | 3 | 309-320 | 10.6000/1929-6029.2014.03.03.10 | 0 | 0.0 | 2 | F |
| Statin compliance in the Umbrian population | European Journal of Clinical Pharmacology | 659-61 | 59 | 2003 | 10.1007/s00228-003-0675-2 | 14508622 | 2.84 | 26 | F |
| Validation of chronic obstructive pulmonary disease (COPD) diagnoses in healthcare databases: a systematic review protocol. | BMJ Open | e011777 | 6 | 2016 | 10.1136/bmjopen-2016-011777 | 27251687 | 2.56 | 0 | C |
| Validity of breast, lung and colorectal cancer diagnoses in administrative databases: a systematic review protocol. | BMJ Open | e010409 | 6 | 2016 | 10.1136/bmjopen-2015-010409 | 26993624 | 2.56 | 1 | F |
| Efficacy of Non-Pharmacological Interventions to Prevent and Treat Delirium in Older Patients: A Systematic Overview. The SENATOR project ONTOP Series. | Plos One | e0123090 | 10 | 2015 | 10.1371/journal.pone.0123090 | 26062023 | 3.05 | 2 | F |
| Deviation from intention to treat analysis in randomised trials and treatment effect estimates: meta-epidemiological study. | BMJ | h2445 | 350 | 2015 | 10.1136/bmj.h2445 | 26016488 | 19.69 | 4 | F |
| Evidence of and recommendations for non-pharmacological interventions for common geriatric conditions: the SENATOR-ONTOP systematic review protocol. | BMJ Open | e007488 | 5 | 2015 | 10.1136/bmjopen-2014-007488 | 25628049 | 2.56 | 7 | F |
| Modified versus standard intention-to-treat reporting: Are there differences in methodological quality, sponsorship, and findings in randomized trials? A cross-sectional study | Trials | 58 | 12 | 2011 | 10.1186/1745-6215-12-58 | 21356072 | 2.49 | 32 | L |
| Modified intention to treat reporting in randomised controlled trials: systematic review. | BMJ | c2697 | 340 | 2010 | 10.1136/bmj.c2697 | 20547685 | 13.47 | 59 | F |

**Project Title:**
Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

# Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

* Position: F=First L=Last C=Corrispondent

**For evaluation CV**

| Title | Publication / Journal | Pag | Vol | Year | DOI | PMID | IF | Cit. |
|---|---|---|---|---|---|---|---|---|
| Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. | BMJ | 18-22 | 327 | 2003 | 10.1136/bmj.327.7405.18 | 12842950 | 19.967 | 131 |
| Statin compliance in the Umbrian population. | European Journal of Clinical Pharmacology | 659-661 | 59 | 2003 | 10.1007/s00228-003-0675-2 | 14508622 | 2.71 | 26 |
| Glycoprotein IIb-IIIa inhibitors for acute ischemic stroke. | Stroke | 1113-1114 | 38 | 2007 | 10.1161/01.STR.0000258356.68323.6d | - | 5.723 | 11 |
| Modified intention to treat reporting in randomised controlled trials: Systematic review. | BMJ | 33 | 340 | 2010 | 10.1136/bmj.c2697. | 20547685 | 19.967 | 59 |
| Grading quality of evidence and strength of recommendations in clinical practice guidelines Part 3 of 3. the GRADE approach to developing recommendations. | Allergy: European Journal of Allergy and Clinical Immunology | 588-595 | 66 | 2011 | 10.1111/j.1398-9995.2010.02530.x | 21241318 | 6.335 | 48 |
| Deviation from intention to treat analysis in randomised trials and treatment effect estimates: Meta-epidemiological study. | BMJ | h2445 | 350 | 2015 | 10.1136/bmj.h2445. | 26016488 | 19.967 | 4 |
| Fresh frozen plasma for cardiovascular surgery. | Cochrane database of systematic reviews 7: CD007614. | CD007614 | 7 | 2015 | 10.1002/14651858.CD007614.pub2 | 26171897 | 6.103 | 3 |
| Validity of ICD-9-CM codes for breast, lung and colorectal cancers in three Italian administrative healthcare databases: A diagnostic accuracy study protocol. | BMJ Open | e010547 | 6 | 2016 | 10.1136/bmjopen-2015-010547 | 27016247 | 2.562 | 1 |
| Validity of breast, lung and colorectal cancer diagnoses in administrative databases: A systematic review protocol. | BMJ Open | e010409 | 6 | 2016 | 10.1136/bmjopen-2015-010409 | 26993624 | 2.562 | 1 |
| Validation of chronic obstructive pulmonary disease (COPD) diagnoses in healthcare databases: A systematic review protocol. | BMJ Open | e011777 | 6 | 2016 | 10.1136/bmjopen-2016-011777 | 27251687 | 2.562 | 0 |

**Project Title:**
Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

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**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

**Grant**

| Funded Institution / Country | Year | Title | Position in Projects | Fund ( € ) | Source / Funding Inst. | Att.* |
|---|---|---|---|---|---|---|
| Ministry of Health, Italy | November 2011 | Impact of Modified Intention to Treat Reporting on Treatment Effect in Metaanalyses: A MetaEpidemiological Study | Coordinator | 65000 | http://www.salute.gov.it/imgs/C_17_pagineAree_4517_listaFile_itemName_4_file.pdf | Yes |

* Attached Certification Letter

**Certification letter:** Abraha_Grant.pdf

**Project Title:**
Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Biographical Sketch Contributors 1

**Name:**
Di Furia Lucia

Institution: Marche
Department/Unit: Healthcare Service Directorate, Regional Health Authority of Umbria
Position Title: Director

| Education/Training - Institution and Location | Degree | Year(s) | Field of study |
|---|---|---|---|
| University Politecnica delle Marche Faculty of Economics Giorgio Fuà (Ancona, italy) | Master (II level) in the Management of the Health Sector 110/110 cum laude | 2 | Economics, rules and regulations of the health sector, psychology of the organisation; organisation and control, financial administration, networking |
| University Politecnica delle Marche, Faculty of Medicine (Ancona, Italy) | Post-graduate in Psychiatry (50/50 cum laude) | 5 | Suicidal behavior in drug addiction. Study in a population of opiate addicts |
| University Politecnica delle Marche, Faculty of Medicine (Ancona, Italy) | PhD in Oncology | 3 | In vitro toxicity of purine nucleosides in solid tumors |
| University Politecnica delle Marche, Faculty of Medicine (Ancona, Italy) | Post-graduate in Oncology (50/50 cum laude) | 4 | Correlation between the clinical and the anatomy-pathological picture in patients with cancer. |
| University Politecnica delle Marche, Faculty of Medicine (Ancona, Italy) | Degree in Medicine (1985) | 6 | Medicine and surgery |

**Personal Statement:**

I have expertise in different fields including research based on randomized and observational studies. My recent experience was in the organization, control and evaluation in the healthcare system in the Marche region. In this project I will lead the Marche team in the process of validation of the administrative database within the Marche region and ensure collaboration with the PI.

**Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

| Institution | Division / Research group | Location | Position | From year | To year |
|---|---|---|---|---|---|
| Regional Health Office - Marche Region | Executive for Hospital care, Emergency-urgency, Research and Training. | Marche Region, Ancona, Italy | Medical Manager. In charge of clinical charts, tariffs, waiting lists, specialised care in the community, out of region mobility. | 2013 | 2016 |
| Regional Health Office - Marche Region | Executive for Research, Innovation and Training | Marche Region, Ancona, Italy | Medical Manager | 2011 | 2013 |
| Health Service - Marche region | Operational management of Research, Innovation, Specialised care in the community and Oncology | Marche Region, Ancona, Italy | Medical Manager ad interim for Public Health | 2009 | 2011 |
| Health Service - Marche Region | Drug addiction; Mental Health; Oncology | Marche Region, Ancona, Italy | Medical Manager ad interim for Public Health | 2005 | 2009 |
| Local Health Unit AUSL 16, Padova, Italy | Drug Addiction Department | Padova, Italy | Medical Doctor | 1994 | 2005 |
| Local Health Unit of Ancona, Italy | Radiotherapy | Ancona, Italy | Medical Doctor | 1991 | 2004 |

## Awards and Honors

**Official H index:** 12.0

**Source:** Scopus **Scopus Author Id:** 34167627000

**ORCID ID:** - **RESEARCH ID:** -

**Awards and Honors:**

Previously member of the ECCAS (European Collaborating Centres in Addiction Studies)
Previously Member of the Research and Innovation working group of the Servizio Salute-Regione Marche
Substitute member of LEA commission for Italian Ministry of Health.
Member of National commission on Observatory in Medicine Specialization (MIUR n.195/2015);
Member of National commission on Observatory on Continuing education in Medicine
Project Manager for the European health projects: ReDNet (Health Programme 2009); REDUCE; JADE (FP 7; AGES 2.0; IRHOLA; AGL - Active Ageing Going Local (PROGRESS 2007-2013).

**Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Biographical Sketch Contributors 2

**Name:**
Spazzafumo Liana

Institution: Marche
Department/Unit: Healthcare Service Directorate, Regional Health Authority of Marche
Position Title: Collaborator

| Education/Training - Institution and Location | Degree | Year(s) | Field of study |
|---|---|---|---|
| Università degli Studi di Ancona | B.S. | 5 | Economics |

**Personal Statement:**

I have an extensive experience within the INRCA Institute in providing statistical analysis, modelling and programming in different types of studies including randomized and observational studies and in different fields such as biochemistry, genetics and cardiovascular area. I am now appointed in the Marche region to manage the administrative database. I will plan and conduct (in conjunction with Paolo Eusebi) the proposed statistical model within the cohort of patients identified within the Marche administrative database.

| Institution | Division / Research group | Location | Position | From year | To year |
|---|---|---|---|---|---|
| INRCA - IRCSS | Epidemiologic Observatory - ARS Marche | Ancona | Head | 2014 | 2016 |
| INRCA - IRCCS | Laboratory of Studies and Research in Biostatistics | Ancona | Head | 2010 | 2014 |
| INRCA - IRCCS | Biometry and Medical Statistics Centre | Ancona | Head | 1992 | 2009 |
| INRCA - IRCCS | - | Ancona | Teaching activity in two training projects "Epidemiology and Clinical Trials in Geriatrics" | 2010 | 2011 |
| Società Italiana di Chirurgia Colorettale (SICCR) and Università Cattolica di Roma | - | Roma | Professor of Applied Medical Statistics | 2007 | 2010 |
| INRCA - IRCCS | - | Ancona, Italy | Collaboration to the strategic institutional project: "Multidimensional assessment of frail elderly" | 2005 | 2007 |

## Awards and Honors

**Official H index:** 25.0

**Source:** Scopus

**Scopus Author Id:** 6701756976

**ORCID ID:** orcid.org/0000-0002-9718-1658

**RESEARCH ID:** E-5488-2015

**Awards and Honors:**

| | |
|---|---|
| | **Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation |
| **Project Code:** RF-2016-02363990 | **Principal Investigator:** Abraha Iosief |
| **Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4 | **Applicant Institution:** Umbria |

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

1. Bioethics Committee INRCA 2010-2014 as a biostatistician (2012-2014).
2. INRCA coordination for the European project "Genetics of Healthy Aging (GEHA)" from 2006 to 2009 (funding: EUR 124,000).
3. Winner of the Italian Ministry of Health grant 2007: "Multi-disciplinary Rehabilitative Models: new drugs for elderly patients with chronic heart failure". Unit of Biostatistics INRCA - Ancona (funding: EUR 45,000)
4. Winner of Young Researcher (Ministry of Health) 2009 "Psychological consequences of cancer in the elderly and in his family" - Unit of Biostatistics INRCA (EUR 29,000)

**Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Biographical Sketch Contributors 3

**Name:**
Eusebi Paolo

Institution: Umbria
Department/Unit: Health Planning Office, Regional Health Authority of Umbria
Position Title: Research Assistant

| Education/Training - Institution and Location | Degree | Year(s) | Field of study |
|---|---|---|---|
| University of Perugia | Postdoctoral training | 3 | Biostatistics and Epidemiology |
| University of Perugia | Ph.D. | 4 | Mathematics and Statistics |
| University of Perugia | B.S. | 5 | Economics |

**Personal Statement:**

I have the expertise and motivation necessary to carry out the proposed work relative to all the statistical aspects. I have a broad background in biostatistics and data management with specific training and expertise in key research areas for this application. In particular I have analysed data of several observational studies in which I have successfully applied novel approaches for dealing with selection bias, confounding, and missing data. I have also collaborated in research group involved in research for using administrative databases for delivering better decisions in healthcare.

| Institution | Division / Research group | Location | Position | From year | To year |
|---|---|---|---|---|---|
| University of Perugia | Neurology Clinic | Perugia, Italy | Statistician | 2014 | 2016 |
| Ethical Review Board of Umbria | - | Perugia, Italy | Member of Ethical Review Board of Umbria | 2010 | 2014 |
| Regional Health Authority of Umbria | Epidemiology Department | Perugia, Italy | Statistician | 2008 | 2014 |
| University of Perugia | Department of Economics, Finance and Statistics | Perugia, Italy | Post-Doc: "Measuring health conditions and functional independence on elderly population and evaluating health and social care". | 2005 | 2008 |
| University of Perugia | Department of Economics, Finance and Statistics | Perugia | Fellowship: "Item Response Theory Models with covariates". | 2004 | 2005 |

## Awards and Honors

**Official H index:** 15.0

**Source:** Scopus

**Scopus Author Id:** 24477129600

**ORCID ID:** orcid.org/0000-0002-0715-6396

**RESEARCH ID:** O-2721-2013

**Awards and Honors:**

| | |
|---|---|
| | **Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation |
| **Project Code:** RF-2016-02363990 | **Principal Investigator:** Abraha Iosief |
| **Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4 | **Applicant Institution:** Umbria |

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

1. Associate Editor of BMC Medical Research Methodology (Springer).
2. Referee for BMJ Open, Diabetes Care, Biometrical Journal, Social Indicators Research, BMC Medical Research Methodology, Journal of Applied Statistics, Scientific Reports, Journal of Clinical Epidemiology, Statistica Applicata.
3. Winner of the Italian Ministry of Health grant (GR-2013-02357757) as PI of the project: "Biostatistical methods for meta-analyzing individual participant data in diagnostic and prognostic research, with application to the role of cerebrospinal fluid biomarkers in Parkinson's disease".

**Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Biographical Sketch Contributors 4

**Name:** Orso Massimiliano

Institution: Umbria
Department/Unit: Health Planning Service
Position Title: Collaborator

| Education/Training - Institution and Location | Degree | Year(s) | Field of study |
|---|---|---|---|
| Università Cattolica del Sacro Cuore, Rome, Italy. | Master of Science | 1 | Epidemiology and Biostatistics |
| Link Campus University, Rome, Italy. | BA | 3 | Public Administration |
| Università di Perugia, Perugia, Italy. | Specialist Degree | 2 | Public and Business Communication |
| Università di Perugia, Perugia, Italy. | BA | 3 | Communication sciences |

**Personal Statement:**

I have recently acquired sufficient experience in the field of methodology. I have collaborated in a meta-epidemiological study that was able to identify the modified intention-to-treat as a source of bias. I am currently working on validating ICD-9 codes in the field of oncology within the administrative database of Marche. Within the present I will collaborate in the identification of case definition of diseases, development of checklist and appropriate data abstract forms, data abstraction and analysis. I have the motivation necessary to successfully collaborate in the proposed work

| Institution | Division / Research group | Location | Position | From year | To year |
|---|---|---|---|---|---|
| University of Perugia | Cardiology and cardiovascular pathophysiology | Perugia, Italy | Research fellow | 2015 | 2016 |
| Regional Health Authority of Umbria | Health Planning Service | Perugia, Italy | Fellowship: Research Project "MIDDIR - Methods for investments/disinvestments and distribution of health technologies in Italian Regions". | 2013 | 2014 |
| Regional Health Authority of Umbria | Health Planning Service | Perugia, Italy | Fellowship: "Collaboration program to develop the Interregional Network for the systematic assessment of health technologies - HTA (RIHTA)". | 2012 | 2013 |

## Awards and Honors

**Official H index:** 1.0

**Source:** Scopus

**Scopus Author Id:** 56716506800

**ORCID ID:** orcid.org/0000-0003-0200-1202

**RESEARCH ID:** -

| | |
|---|---|
| | **Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation |
| **Project Code:** RF-2016-02363990 | **Principal Investigator:** Abraha Iosief |
| **Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4 | **Applicant Institution:** Umbria |

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

**Awards and Honors:**

-

**Project Title:**
Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

# Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Expertise Research Collaborators

**Selected peer-reviewed publications of the Research Group / Collaborators**

| Collaborator | Title | Publication / Journal | Pag | Vol | Year | DOI | PMID | IF | Cit. |
|---|---|---|---|---|---|---|---|---|---|
| Di Furia Lucia | MDMA ('ecstasy') consumption in the context of polydrug abuse: A report on 150 patients | Drug and Alcohol Dependence | 85-90 | 52 | 1998 | 10.1016/S0376-8716(98)00051-9 | 9788011 | 3.278 | 177 |
| Spazzafumo Liana | A manual of guidelines to score the modified Cumulative Illness Rating Scale and its validation in acute hospitalized elderly patients | Journal of the American Geriatrics Society | 1926-1931 | 56 | 2008 | 10.1111/j.1532-5415.2008.01935.x | 18811613 | 3.842 | 112 |
| Spazzafumo Liana | Circulating microRNAs are new and sensitive biomarkers of myocardial infarction | European Heart Journal | 2765-2773 | 31 | 2010 | 10.1093/eurheartj/ehq167 | 20534597 | 15.064 | 306 |
| Di Furia Lucia | Mephedrone (4-methylmethcathinone; 'Meow meow'): Chemical, pharmacological and clinical issues | Psychopharmacology | 593-602 | 214 | 2011 | 10.1007/s00213-010-2070-x | 21072502 | 3.54 | 168 |
| Eusebi Paolo | Underrecognition and Undertreatment of Dementia in Italian Nursing Homes | Journal of the American Medical Directors Association | 759.e7-759.e13 | 13 | 2012 | 10.1016/j.jamda.2012.05.015 | 22727993 | 6.616 | 15 |
| Spazzafumo Liana | Diagnostic potential of circulating miR-499-5p in elderly patients with acute non ST-elevation myocardial infarction | International Journal of Cardiology | 531-536 | 167 | 2013 | 10.1016/j.ijcard.2012.01.075 | 22330002 | 4.638 | 61 |
| Eusebi Paolo | Latent class bivariate model for the meta-analysis of diagnostic test accuracy studies | BMC Medical Research Methodology | 88 | 14 | 2014 | 10.1186/1471-2288-14-88 | 25015209 | 3.059 | 5 |
| Eusebi Paolo | Anticholinergic Drug Use and Negative Outcomes Among the Frail Elderly Population Living in a Nursing Home | Journal of the American Medical Directors Association | 825-829 | 15 | 2014 | 10.1016/j.jamda.2014.08.002 | 25282629 | 6.616 | 14 |
| Eusebi Paolo | Predictors of Functional Changes in Italian Nursing Home Residents: The U.L.I.S.S.E. Study | Journal of the American Medical Directors Association | 306-311 | 17 | 2015 | 10.1016/j.jamda.2015.11.004 | 26715356 | 6.616 | 0 |
| Orso Massimiliano | Document Diagnostic utility of CSF alpha-synuclein species in Parkinson's disease: Protocol for a systematic review and meta-analysis | BMJ Open | 011113 | 6 | 2016 | 10.1136/bmjopen-2016-011113 | 27297011 | 2.562 | 0 |

**Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

**Grant**

| Funded Institution / Country | Year | Title | Position in Projects | Fund ( € ) | Collaborator | Source / Funding Inst. | Att.* |
|---|---|---|---|---|---|---|---|
| Ministry of Health, Italy | 2013 | Biostatistical methods for meta-analyzing individual participant data in diagnostic andprognostic research, with application to the role of cerebrospinal fluid biomarkers in Parkinson's disease. | Coordinator | 170508 | Di Furia Lucia | http://www.salute.gov.it/imgs/C_17_pagineAree_4357_listaFile_itemName_12_file.pdf | Yes |
| European Union | 2011 | Reducing hepatitis C sexual and drug taking risk behaviours among female drug users in Europe (REDUCE): translating evidence into practice. | Coordinator | 97305 | Di Furia Lucia | https://thereduceproject.imim.es/partners.html | No |
| European Union | 2012 | Intervention Research On Health Literacy among Ageing population Acronimo: IROHLA | Coordinator | 88320 | Di Furia Lucia | http://www.irohla.eu/partners/partners/ | No |
| European Union | 2012 | AGES 2.0: Activating and Guiding the Engagement of Seniors through social media | Coordinator | 928661 | Di Furia Lucia | http://www.ages2.eu/en/contacts | No |
| European Union | 2013 | Active Ageing Going Local ¿ a multi-stakeholder approach for three Italian Regions | Coordinator | 291243 | Di Furia Lucia | http://www.agl-project.eu/contacts/ | No |

* Attached Certification Letter (Y/N)

**Certification letter:** Eusebi_Grant.pdf

**Project Title:**
Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation

**Project Code:** RF-2016-02363990

**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

## Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

**Proposed total budget ( Euro )**

| Costs | Budget Year 1 | Budget Year 2 | Budget Year 3 | TOTAL BUDGET | Co-Funding | List of costs proposed for funding to the moh |
|---|---|---|---|---|---|---|
| 1 Staff salary | 120.000,00 | 120.000,00 | 120.000,00 | 360.000,00 | 360.000,00 | |
| 2 Researchers contracts | 60.000,00 | 60.000,00 | 60.000,00 | 180.000,00 | 0,00 | 180.000,00 |
| 3a Equipment (leasing) | 4.000,00 | 4.000,00 | 4.000,00 | 12.000,00 | 0,00 | 12.000,00 |
| 3b Supplies | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 |
| 3c Model costs | 27.000,00 | 40.000,00 | 20.000,00 | 87.000,00 | 20.000,00 | 67.000,00 |
| 4 Subcontracts | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 |
| 5 Patient costs | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 |
| 6 IT services and data bases | 10.000,00 | 30.000,00 | 30.000,00 | 70.000,00 | 0,00 | 70.000,00 |
| 7 Travels | 1.000,00 | 4.000,00 | 2.600,00 | 7.600,00 | 0,00 | 7.600,00 |
| 8 Pubblication costs | 2.000,00 | 2.000,00 | 3.600,00 | 7.600,00 | 0,00 | 7.600,00 |
| 9 Training and Dissemination | 1.000,00 | 1.000,00 | 1.800,00 | 3.800,00 | 0,00 | 3.800,00 |
| 10 Overheads | 10.000,00 | 10.000,00 | 12.000,00 | 32.000,00 | 0,00 | 32.000,00 |
| 11 Coordination costs | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 |
| **Total** | 235.000,00 | 271.000,00 | 254.000,00 | 760.000,00 | 380.000,00 | 380.000,00 |

Report the Co-Funding Contributor:

Regione Umbria and Regione Marche

| | |
|---|---|
| | **Project Title:** Enhancing the Validity of Administrative Healthcare Databases for Disease Surveillance, Comparative Effectiveness Research and Safety Evaluation |
| **Project Code:** RF-2016-02363990 | **Principal Investigator:** Abraha Iosief |
| **Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4 | **Applicant Institution:** Umbria |

# Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Budget Justification

| | |
|---|---|
| 1 Staff salary | Salary of 2 (0.5 FTE) senior researchers of Regione Umbria and 2 (0.25) FTE senior researchers of Region Marche |
| 2 Researchers contracts | 2 junior researchers (1 FTE); junior researchers will receive adequate training in healthcare services research methodology and pharmaco-epidemiology, and will take part in each phase of the project; |
| 3a Equipment (leasing) | adequate hardware facilities and specific software to conduct the research will be acquired; |
| 3b Supplies | not foreseen; |
| 3c Model costs | selection and retrieving of medical charts; |
| 4 Subcontracts | not foreseen; |
| 5 Patient costs | not foreseen; |
| 6 IT services and data bases | Implementation and maintenance of a specific database for data collection and statistical analyses. |
| 7 Travels | national and international congress registration and traveling allowances. |
| 8 Pubblication costs | "costs relating to English language-editing and editorial submissions of preliminary and final results to international peer-review journals will be covered under this heading;" |
| 9 Training and Dissemination | adequate training will be provided to researchers involved in the project; |
| 10 Overheads | costs incurred for the research in relation to general operating expenses; |
| 11 Coordination costs | not foreseen; |

**Project Title:**
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**Principal Investigator:** Abraha Iosief

**Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4

**Applicant Institution:** Umbria

# Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Proposed budget distribution ( Euro )

| Costs | Unit 1 Total Budget | Unit 1 costs MOH funding | Unit 2 Total Budget | Unit 2 costs MOH funding | Unit 3 Total Budget | Unit 3 costs MOH funding |
|---|---|---|---|---|---|---|
| 1 Staff salary | 180.000,00 | | 180.000,00 | | 0,00 | |
| 2 Researchers contracts | 90.000,00 | 90.000,00 | 90.000,00 | 90.000,00 | 0,00 | 0,00 |
| 3a Equipment (leasing) | 6.000,00 | 6.000,00 | 6.000,00 | 6.000,00 | 0,00 | 0,00 |
| 3b Supplies | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 |
| 3c Model costs | 43.500,00 | 33.500,00 | 43.500,00 | 33.500,00 | 0,00 | 0,00 |
| 4 Subcontracts | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 |
| 5 Patient costs | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 | 0,00 |
| 6 IT services and data bases | 35.000,00 | 35.000,00 | 35.000,00 | 35.000,00 | 0,00 | 0,00 |
| 7 Travels | 3.800,00 | 3.800,00 | 3.800,00 | 3.800,00 | 0,00 | 0,00 |
| 8 Pubblication costs | 3.800,00 | 3.800,00 | 3.800,00 | 3.800,00 | 0,00 | 0,00 |
| 9 Training and Dissemination | 1.900,00 | 1.900,00 | 1.900,00 | 1.900,00 | 0,00 | 0,00 |
| 10 Overheads | 16.000,00 | 16.000,00 | 16.000,00 | 16.000,00 | 0,00 | 0,00 |
| 11 Coordination costs | 0,00 | 0,00 | | | | |
| **Total** | 380.000,00 | 190.000,00 | 380.000,00 | 190.000,00 | 0,00 | 0,00 |

Legend
Unit 1: Umbria
Unit 2: Marche
Unit 3: Marche

| | |
|---|---|
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| **Research Type:** b) Change-promoting: valutare la sicurezza, efficacia, costo-efficacia, di trattamenti/tecnologie/interventi sanitari per cui sussistano significativi margini di incertezza relativamente agli aspetti menzionati, anche con studi clinici di fase 3 e 4 | **Applicant Institution:** Umbria |

# Project Type: Ordinary/Progetti ordinari di Ricerca Finalizzata

## Principal Investigator Data

Cognome: Abraha
Nome: Iosief
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Struttura: Servizio Programmazione Socio Sanitaria dell'Assistenza di Base ed Ospedaliera
Istituzione: Regione Umbria