

The CRACK programme: a scientific alliance for bridging healthcare research and public health policies in Italy

GIOVANNI CORRAO^(1,2), GIANCARLO CESANA^(1,2), CARLO LA VECCHIA^(3,4), GIORGIO VITTADINI^(1,5), ALBERICO CATAPANO^(6,7), GIUSEPPE MANCIA^(8,9) FOR THE SCIENTIFIC BOARD; OVIDIO BRIGNOLI⁽¹⁰⁾, ALESSANDRO FILIPPI⁽¹⁰⁾, LUIGI CANTARUTTI⁽¹¹⁾ FOR THE GENERAL AND PAEDIATRIC PRACTITIONER BOARD, LUCA MERLINO⁽¹²⁾, CARLO ZOCCHETTI⁽¹²⁾, FLAVIA CARLE^(13,14) FOR REGIONAL AND CENTRAL HEALTH AUTHORITIES

ABSTRACT

Healthcare utilisation databases, and other secondary data sources, have been used with growing frequency to assess health outcomes and healthcare interventions worldwide. Their increased popularity as a research tool is due to their timely availability, the large patient populations covered, low cost, and applicability for studying real-world clinical practice. Despite the need to measure Italian National Health Service performance both at regional and national levels, the wealth of good quality electronic data and the high standards of scientific research in this field, healthcare research and public health policies seem to progress along orthogonal dimensions in Italy. The main barriers to the development of evidence-based public health include the lack of understanding of evidence-based methodologies by policy makers, and of involvement of researchers in the policy process. The CRACK programme was launched by some academics from the Lombardy Region. By extensively using electronically stored data, epidemiologists, biostatisticians, pharmacologists and clinicians applied methods and evidence to several issues of healthcare research. The CRACK programme was based on their intention to remove barriers that thwart the process of bridging methods and findings from scientific journals to public health practice. This paper briefly describes aim, articulation and management of the CRACK programme, and discusses why it might find articulated application in Italy.

Key words: Comparative Effectiveness Research; Healthcare Utilization Database; Medical records; Evidence-based public health

(1) Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Milan, Italy

(2) Centre for Public Health, University of Milano-Bicocca, Milan, Italy

(3) Department of Epidemiology, IRCCS Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy

(4) Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

(5) Centro di Ricerca Interuniversitario per i Servizi di Pubblica Utilità (CRISP), University of Milano-Bicocca, Milan, Italy

(6) Department of Pharmacological Sciences, University of Milan, Milan, Italy

(7) Centre for Pharmacoepidemiology and Pharmacoutilsation, University of Milano, Milan, Italy

(8) IRCCS Istituto Auxologico Italiano, Milan, Italy

(9) Centre for Clinical Physiology and Hypertension, University of Milano-Bicocca, Milan, Italy

(10) Italian College of General Practitioners, Italy, Health Search, Florence, Italy

(11) Family Paediatrician Pedianet Project, Padua, Italy

(12) Operative Unit of Territorial Health Services, Lombardy Regional Administration, Milan, Italy

(13) Unit of Health Management, Italian Ministry of Health, Rome, Italy

(14) Centre for Epidemiology, Biostatistics and Medical Information Technology, Polytechnic University of Marche, Ancona, Italy

CORRESPONDING AUTHOR: Giovanni Corrao, Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, University of Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Building U7, 20126 Milan, Italy. Tel: +39 02 64485854.

Fax: +39 02 64485899. e-mail: giovanni.corrao@unimib.it

DOI: 10.2427/8980

FROM BIG DATA TO COMPARATIVE EFFECTIVENESS RESEARCH

The amount of data being digitally collected and stored is vast and rapidly expanding. Computer scientists introduced the term “big data” to describe this evolving technology. Big data has been successfully used in astronomy (e.g., the Sloan Digital Sky Survey of information provided by the telescope), retail sales (e.g., Walmart’s expansive number of transactions), search engines (e.g., Google’s customisation of individual searches based on previous web data), and politics (e.g., a campaign’s focus of political advertisements on people most likely to support their candidate based on web searches) [1].

In this paper we discuss the potential of big data in the field of healthcare research. Healthcare databases are attractive because they put large quantities of data into our hands. But let us be ready to say no to quantity if the quality impairment is too great. Both Weiss [2] and Ray [3] provide examples in which debatable eligibility criteria, incompleteness or incorrectness of linkage variables and ascertainment of exposure and outcome, and presence of confounding, resulted in incorrect conclusions.

We already pointed out that big data generated from healthcare utilisation databases and other secondary data sources should be regarded not only as a technological tool for storing and managing said data, but also, perhaps mainly, as a methodological challenge for building reliable evidence, which means converting data into information and know-how to facilitate healthcare decision-making. Comparative effectiveness research is the answer to this demand [4, 5], and extraordinary methodological advancements on this issue have been achieved during the past few decades [6-12].

COMPARATIVE EFFECTIVENESS RESEARCH FOR HEALTHCARE MANAGEMENT: LESSONS FROM THE US AND THE UK

In the United States, in the UK, as well as in many others countries, decisions based on the principles of evidence-based healthcare have guided healthcare practice, education, and

policy for over 25 years [13]. The core principle of evidence-based healthcare is that decisions should be made using the best available scientific evidence [14].

In many cases, there may be a gradient of actions that could be taken based on available evidence. *Quanstrum & Hayward* discussed this gradient and argued that healthcare decision-making is changing, mainly because more information is available about treatment options [15]. In such conditions, decisions on healthcare treatment cannot be based on a threshold above which treatment is always considered beneficial and recommendable. Rather, there is almost always a large zone of choice where health benefits of a given treatment may be high and economically sustainable for a given population, but this might not be the case for other ones. This makes the decision-making process more complex than a “simple” evidence-based algorithm. In other words, the critical appraisal of all relevant research, as done in a systematic review of literature, is always necessary to make decisions [16, 17] because we must know whether a given treatment is expected to generate health benefits according to the best available knowledge. This knowledge is, however, often inadequate because it does not specify the impact of that treatment under the usual circumstances of healthcare practice. This justifies the great consideration gained by comparative effectiveness research during the last few decades as a key healthcare management tool.

Perhaps, the main evidence of this is the fact that comparative effectiveness research has been enshrined in the US Healthcare Reform Law of 2010 [18, 19]. The law mandates the creation of a Patient-Centred Outcomes Research Institute (PaCORI), which will establish national research priorities and methodological standards, and will carry out research. The UK’s National Institute for Health and Clinical Excellence, which was established in 1999, was the world pioneer in this area [20]. Though the organisational structure and duties of the American and British Institutes vary (e.g., the US Institute is barred by law from considering the cost-effectiveness of interventions), both institutes have an overarching common goal: to improve public health through research on the relative effectiveness of different interventions [1].

BRIDGING HEALTHCARE RESEARCH AND PUBLIC HEALTH POLICIES: AN ITALIAN OUTLOOK

There are at least three good reasons to consider Italy an ideal country for experiencing structured initiatives bridging healthcare research and public health policies.

In the first place, the Italian National Health Service (NHS) provides universal coverage entitling all citizens to equal access to “essential” healthcare services, which are provided either free of charge or at a minimal charge [http://www.salute.gov.it/portale/salute/p1_5.jsp?lingua=italiano&id=111&area=IL_Ssn]. The NHS is structured into three hierarchical tiers of public authority: central government, regions, and local health authorities, namely geographically based health management organisations responsible for providing comprehensive care to a defined population [21]. The Italian Constitution (Art. 117) and the following legislative decrees [e.g., D.Lgs Sept, 18 2001, n.347 <http://www.trovanorme.salute.gov.it/dettaglioAtto?id=12119&completo=true>], assign the central government the duty of defining “essential” healthcare services, which must be warranted to all citizens [http://www.salute.gov.it/portale/salute/p1_5.jsp?lingua=italiano&id=111&area=IL_Ssn] and of monitoring use and impact of healthcare supplied and equity in access to healthcare services throughout Italy. The same laws decree that service management, healthcare services supplied and resource allocation must be wholly warranted to Regional Administrations for autonomous management. This implies the central government and regional authorities’ need for data, information and evidence to differentiate the decision-making process by competent territorial level and specific function.

Secondly, population-based secondary data sources have proliferated in Italy during the past few decades. Among these, regional healthcare utilisation databases that collect data for healthcare delivery system management would be a valuable resource for healthcare research. These are resources that many US health policy and health service researchers would like to find in their own country [22]. In fact, unlike US administrative databases, electronic archives used by the Italian healthcare system offer non-fragmented coverage of practically all the resident population. In addition, Italian

healthcare utilisation databases have now reached a degree of completeness and quality that enhances the potential of that data and interest in the same to build reliable evidence in the field of comparative healthcare research.

Besides healthcare utilisation databases, enterprises networking general practitioners to create research-oriented medical records databases is a consolidated practice in Italy today. The most prominent among these, the so-called Thales - Health Search database (i.e., the Italian analogue of the British GPRD), receives data from more than 700 general practitioners (GP) and covers almost 2.1% of the Italian population [<http://www.healthsearch.it>]. Other GP databases covering smaller populations provide very high quality data (e.g., the *ULNet* database that currently receives data from approximately 220 GPs operating in the Lombardy Region). In addition, the so-called *Pedianet* database [<http://www.pedianet.it/it/>] is, to our knowledge, the only initiative in the world that, by networking almost 300 paediatricians of first choice (the general practitioner assisting children aged under 18 years in Italy), has created a very useful and unique paediatric database.

In such conditions, rather than contrasting North American and European approaches to real-world (RW) data collecting [23, 24] respectively by administrative databases (e.g., Medicare and Medicaid [25]) and medical records electronic archives (e.g., UK General Practice Research Database [26]), the coverage of large portions of the Italian population by both these sources allows their use and integration, augmenting the available informative potential.

Thirdly, it is an established fact that biostatisticians and epidemiologists are the natural comparative effectiveness researchers; for example, the 2010 US law establishes that the Board of Governors of the Institute shall collectively have scientific expertise in “epidemiology and biostatistics, other than in other scientific fields [27]. In Italy, there is a long and well-established academic tradition in these fields and many researchers are currently involved in methodological and applicative projects focused on using electronic databases as a tool for generating reliable evidence.

Despite the need to measure Italian National Health Service performance both at regional and national levels, the wealth of good quality electronic data and the high

standards of scientific research in this field, healthcare research and public health policies seem to progress along orthogonal dimensions in Italy. The main perceived barriers to the development of evidence-based public health in Italy, as well as in many European countries, include the lack of understanding of evidence-based methodologies by policy makers [28] and of involvement of researchers in the policy process [29].

THE CRACK PROGRAMME

Preliminary remarks

CRACK is the acronym of *Carry out a Repository for Administrative and Clinical data Knotting*. The idea is to create a data repository through the integration of different data sources to address open questions in the framework of important diseases for clinics and public health by underpinning the decision-making process with the principles of evidence-based healthcare. From this perspective, CRACK is both a *technological platform and a basic infrastructure bridging healthcare research and public health policies*.

It should be emphasised that, although the acronym CRACK uses the term repository, it does not imply the transfer of data from the place where they are stored by their owners (e.g., Regional authority or Italian Society of General Medicine) to a single storage site. Instead, the CRACK programme proposes collecting data from several sources according to a specific protocol that is approved by the regional authority and the scientific board (Figure 1). The questions we would like to answer through the use of the repository are related to the incidence and prognosis of diseases (prevalence, incidence, survival), healthcare utilisation patterns and safety, effectiveness and cost-effectiveness profiles in RW clinical practice.

Both, general methodological issues and specific clinical and public health questions will be investigated to enhance the value of regional health data by exploiting them from the decision-maker's point of view. In other words, the main strategic aim of the CRACK programme is to create a flywheel, which allows the regional authority to obtain solid data and strong evidence to address health policies.

The term “flywheel” is justified by the fact that both healthcare authorities and research teams would benefit from the CRACK programme because the former would obtain a “no-cost” tool for addressing health policies, while the latter would find good-quality health data available for scientific purposes. Finally, the CRACK programme is expected to boost methodological and applicative research in the field of comparative effectiveness research. Accordingly, training courses will be carried out within the CRACK programme.

Starting up the CRACK programme

The CRACK programme has been developed in the Lombardy Regional environment, which is not by chance. A wide and articulated system of HCU databases supporting management of the regional health service has been developed in Lombardy since 1997. Databases include:

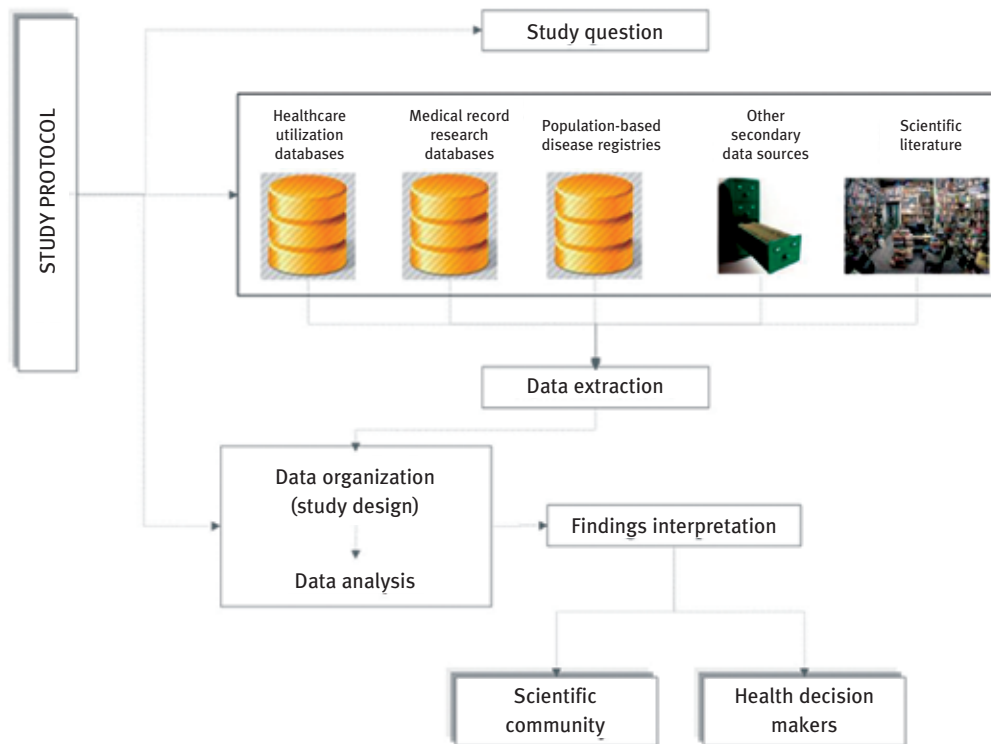
- the archive of residents receiving regional health assistance, practically the whole resident population of about ten million inhabitants, or 16% of the Italian population;
- the HCU databases common to all Italian regions for reimbursement of health service providers (i.e., diagnostic information about hospital discharge from public or private hospitals and outpatient drug prescriptions reimbursable by the NHS);
- a single extensive recording system of health services, such as those concerning access to outpatient specialist and laboratory benefits, mental health services, emergency rooms, delivery assistance, vaccinations, among others.

Data may be linked together by using a unique identification code. In order to preserve privacy, the Lombardy Regional Administration and Privacy Authority agreed to the systematic conversion of the patient's identification code (i.e., the tax code) into an anonymous “encrypted” code. This process prevents the possibility of identifying patients to whom health services are supplied (thus overcoming privacy barriers), while at the same time allowing recognition of each single citizen along his or her entire health track (providing data for healthcare research).

The wide availability of population-based medical record data, such as:

FIGURE 1

ILLUSTRATION OF THE CRACK PROGRAMME FUNCTIONING



- the above reported ULNet general practitioners network,
- and the Lombardy portion of Health Search and Pedianet databases; and disease registries, such as:
 - the six cancer registers of Varese, Milan, Brescia, Como, Mantua and Sondrio accredited by the Italian Association of Cancer Registries [<http://www.registri-tumori.it/cms/?q=node/21#>];
 - and the WHO-MONICA registry of ischemic heart disease and cerebrovascular disease covering the population resident in the Brianza area [30],

make the Lombardy Region particularly attractive for conducting healthcare research based on the use of electronically stored data.

CRACK was launched by some academics from the Lombardy Region. By extensively using electronically stored data, epidemiologists, biostatisticians, pharmacologists and clinicians applied methods and evidence to several issues of healthcare research [see references # 31-69 for papers published in the past 12 months on these issues by the scientific board of the CRACK programme]. The CRACK programme was based on their intention to remove barriers

that thwart the process of bridging methods and findings from scientific journals to public health practice. Concise information on its aims, articulation, management and perspectives is supplied in the following paragraphs.

Aims

The main strategic aim of the CRACK programme is to create a technologic platform and a basic infrastructure that allows regional authorities to obtain solid data and strong evidence to address health policies. The CRACK programme is also expected to boost methodological and applicative research in the field of comparative effectiveness research.

The implementation of a repository of administrative (HCU) and clinical (MR) electronic data covering a given territorial unit (e.g., NHS beneficiaries resident in the Lombardy Region) will be functional to investigate:

- methodological issues: e.g., recognise the sources of systematic uncertainty (mainly misclassification and confounding) when HCU and MR data are used separately, and

implement methods for controlling and/or minimising the effect of such biases by means of integrating HCU and MR data;

- clinical areas: i.e., the management of conditions and diseases that are particularly important for public health (e.g., heart failure, hypertension, dyslipidaemia, type 2 diabetes, cancer, chronic obstructive pulmonary disease, psychiatric, geriatric and paediatric diseases, among others) in RW clinical practice by: (i) assessing the care tracks of patients who start drug therapy for a given condition/disease (including heterogeneity in therapeutic profiles and refill compliance with drug therapies) based on their socio-demographic and clinical features; (ii) estimating the association between care tracks of patients who start drug therapy for a given condition/disease and their risk of experiencing selected clinical outcomes; (iii) providing for cost-effectiveness estimates of care tracks;
- health econometrics and health demand: i.e., providing comprehensive analyses of demand/supply profiles and measuring the level of healthcare quality and expenditure.

Finally, the CRACK programme is expected to facilitate bridging with other European and extra-European countries with the subsequent creation of consortiums that are functional to access research findings.

Articulation

Four working packages form the bearing wall of CRACK architecture.

First, methodological standards for creating the technological platform that underpins the entire programme, including statistical software for data drawing, linking and modelling, are the objective of the **methodological working package**. It must be said that CRACK does not imply the development of a single data container, but rather data collection from several sources according to a specific protocol approved by the regional authority and the scientific board. This will be achieved by carrying out, maintaining and updating an

integrated system useful to (a) collect data from different and heterogeneous sources; (b) extract fields according to their relevance for the study objective, and select records according to predefined inclusion and exclusion criteria; (c) link records according to a specific procedure; (d) organise such data to allow implementation of several observational designs; (e) place such data according to conventional and emerging statistical models; (f) investigate the robustness of findings by varying criteria applied to principal analyses and fitting different models of sensitivity analysis.

Second, the patient-centred investigation of conditions and disease management in the RW clinical practice will constitute the objective of the **clinical working package**. This package will be articulated in clinical areas (e.g., cardiovascular, respiratory and gastrointestinal diseases, diabetes, oncology, mental health, geriatrics, paediatrics, environmental health and drug safety) and, among these, in specific research projects (e.g., exploring the impact of prescribing and substituting generic drugs: the example of cardiovascular therapies; measuring the healthcare burden of diabetes mellitus; clinical use, safety and effectiveness of novel high cost anticancer therapies after marketing approval: a record linkage study).

Third, the service-centred investigation on healthcare system performance (e.g., appropriateness, quality, efficacy and efficiency) and its financial stability will constitute the objective of the **healthcare management working package**. This package will be articulated in specific research projects (e.g., administrative databases as a tool for identifying healthcare demand and costs in a population of over one million).

Finally, with the aim of transferring methods for comparative effectiveness research to NHS staff employed for healthcare database management, as well as to healthcare researchers, the implementation of this **educational working package** is the basic condition for the success of the CRACK programme. There is actually a great need: 1) of knowledge and competencies in this field of research; 2) of standardised methods to guarantee good research practice in the field of observational studies; 3) for healthcare research and public health policies to start speaking common languages and use common methods, thus moving beyond barriers for the

development of evidence-based public health in Italy. With this objective, residential courses will be held on: 1) observational methods (e.g., measures, random and systematic uncertainty, study designing, meta-analysis); 2) biostatistics for epidemiologists (e.g., basic methods and advanced techniques); 3) informative systems for the management of healthcare utilisation databases that are useful for comparative effectiveness research; 4) writing research protocols and technical reports.

Management

Management of the CRACK programme will be assured by two entities that are independent from NHS authorities, as well as from industry pressures, in order to ensure the absence of any conflict of interest.

The first entity is the **scientific board**, which include academic members who are experienced in the field of research methodology (epidemiologists and biostatisticians), public health, medicine and pharmacology. The scientific board would cooperate with public healthcare authorities: 1) in selecting the priority fields, which would be investigated to improve healthcare management; 2) in evaluating research protocols by considering their scientific quality, as well as their relevance in the decision-making process; 3) in coordinating working package activities; 4) in communicating results of healthcare research carried out with administrative databases, with the aim of encouraging the transfer of healthcare research to public health policies. The scientific board will include a small number of fixed members and a variable number of members who will be co-opted for the management of specific projects. Emphasis would be given to the absence of conflicting interests and to documented scientific experience in the field of comparative effectiveness research, especially of fixed members of the scientific board.

The second entity is the **network of accredited laboratories** for data treatment in the fields of competence of the CRACK programme. Accrediting a laboratory means that it must guarantee conformity to: 1) Italian rules for treatment of sensitive data [70]; 2) recommendations for good research practices for retrospective databases to be designed and analysed by the International Society for

Pharmacoeconomics and Outcomes Research (ISPOR) [6-8], as well as by a specific paper of the current issue of EBPH entitled "Building reliable evidence from real-world data: methods, cautiousness and recommendations" [71]. Additionally, regular auditing ensures that confidentiality and good research practice are both guaranteed by accredited laboratories.

PROSPECT

The CRACK programme was conceived and developed in Lombardy, but its structure is clearly suitable for any Italian Region. However, its most interesting application and intriguing challenge should be at the national level.

A distinguishing feature of the Italian NHS is that individual Regions are autonomous in healthcare management, including resource allocation. There is however the need to ensure equal quality and access in healthcare services across the Nation. This last is a priority for Health Ministry. It involves evaluation and comparison of regional health system performances, using a set of validated indicators based on national data flows, followed by national recommendations and guidelines aimed to improve regional health system performances.

National hospital discharge databases have been the main source of health information for a long time. However, in the last few years healthcare focus has shifted from hospital to outpatient settings. Patients are kept as long as possible in their own environment, and transitional care is improved to avoid hospitalization. This entails that additional information is needed to assess health service performances besides hospitalization and other health events. Over the last three years new national data flows have been activated to achieve this goal, but their optimization is heavily influenced by variability of regional databases.

As discussed above, comparative research is critical to devise interventions aimed to improve healthcare quality and efficiency.

Due to variability of regional healthcare systems in Italy, two main aims need to be pursued. The first is enhancing comparative effectiveness research in each Italian region. The second aim is obtaining comparable results in different Regions.

Through implementation of the CRACK programme, the Ministry of Health could provide each Italian region with three important tools to improve healthcare system quality and equity.

The first tool is an equal-for-all, standardized methodology to integrate regional healthcare databases, to obtain validated and comparable performance indicators. Thus, it should be possible to integrate the national set of indicators with information that is difficult, impossible or too expensive to collect through a national data flow. On the other hand, the shared methodology provides useful data to improve completeness and quality of active and future NHS data flows.

The second tool is an equal-for-all, standardized methodology to use regional healthcare databases to generate comparable data as well as solid scientific evidence to assess equity in healthcare service access and effectiveness, safety and sustainability of

diagnostic-therapeutic journeys in RW clinical practice. This would enable regional authorities and national government to work together on the same data and to orient decisions towards evidence-based healthcare principles.

The third tool is the educational working package of the CRACK programme, which should help disseminate good comparative effectiveness research practices and correct use of research results methods among healthcare researchers and operators and among health policymakers at all NHS levels: local, regional and central government authorities.

The National Agency for Regional Health Services (AGENAS) is aimed to connect Health Ministry and Regions, supporting decision-making on government policies in NHS strategies. The CRACK program could help optimize the joint action of the Health Ministry and AGENAS, supporting the evidence-based decision-making process and its adaptation to different NHS levels and functions.

References

- [1] The inevitable application of big data to health care. *JAMA* 2013; 309: 1351-2
- [2] Weiss NS. The new world of data linkages in clinical epidemiology: Are we being brave or foolhardy? *Epidemiology* 2011; 22: 292-4
- [3] Ray WA. Improving automated database studies. *Epidemiology* 2011; 22: 302-4
- [4] Schneeweiss S. Developments in post-marketing comparative effectiveness research. *Clin Pharmacol Ther* 2007; 82: 143-56
- [5] Schneeweiss S, Gagne JJ, Glynn RJ. Assessing the Comparative Effectiveness of newly marketed medications: methodological challenges and implications for drug development. *Clin Pharmacol Ther* 2011; 90: 777-90
- [6] Berger ML, Mamdani M, Atkins D, et al. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: The ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report-Part I. *Value in Health* 2002; 12: 1044-52
- [7] Cox E, Martin BC, Van Staa T, et al. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: The International Society for Pharmacoeconomics and Outcomes Research Good Research. Practices for retrospective database analysis task force report-Part II. *Value Health* 2009; 12: 1053-61
- [8] Johnson ML, Crown W, Martin BC, et al. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources. The International Society For Pharmacoeconomics and Outcomes Research Good Research. Practices for retrospective database analysis task force report-Part III. *Value Health* 2009; 12: 1062-73
- [9] Sox HC, Goodman SN. The methods of comparative effectiveness research. *Annu Rev Public Health* 2012; 33: 425-45
- [10] Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005; 58: 323-37
- [11] Lohr KN. Emerging methods in comparative effectiveness and safety. symposium overview and summary. *Med Care* 2007; 45: S5-S8
- [12] Schneeweiss S. Developments in post-marketing comparative effectiveness research. *Clin Pharmacol Ther* 2007; 82: 143-56
- [13] Montori VM, Guyatt GH. Progress in evidence-based medicine. *JAMA* 2008; 300: 1814-6
- [14] Agency for Healthcare Research and Quality (AHRQ). Developing a protocol for observational comparative

- effectiveness research (OCER): a user's guide. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/research-DRAFT-COPY_AllChapters.pdf
- [15] Quanstrum KH, Hayward RA. Lessons from the mammography wars. *N Engl J Med* 2010; 363: 1076-9
- [16] Bero LA, Jadad AR. How consumers and policy makers can use systematic reviews for decision making. *Ann Intern Med* 1997; 127: 37-42
- [17] Murthy L, Shepperd S, Clarke MJ, et al. Interventions to improve the use of systematic reviews in decision-making by health system managers, policy makers and clinicians. *Cochrane Database Syst Rev* 2012; 9:CD009401
- [18] 111th U.S. Congress. The Patient Protection and Affordable Care Act. Public Law March 23 2010: 111-148
- [19] 111th U.S. Congress. Health Care and Education Reconciliation Act. Public Law March 30 2010: 111-152
- [20] Kelly M, Morgan A, Ellis S, et al. Evidence based public health: A review of the experience of the National Institute of Health and Clinical Excellence (NICE) of developing public health guidance in England. *Soc Sci Med* 2010; 71: 1056-62
- [21] Maio V, Manzoli L. The Italian Health Care System: W.H.O. ranking versus public perception. *Pharm Therap* 2002; 27: 301-8
- [22] Louis DS, Yuen EJ, Maio V, et al. A population-based longitudinal healthcare database in the Emilia-Romagna Region, Italy: A resource for planning and research. *Health Policy Newsletter* 2005; 18: 1-4
- [23] Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects-advantages and disadvantages. *Nature Clinical Practice Rheumatology* 2007; 3: 725-32
- [24] Strom BL. Overview of automated databases in pharmacoepidemiology. In: *Pharmacoepidemiology* (4th edn). Strom BL (ed). Wiley, New York, 2005; 219-22
- [25] Hennessy S, Carson JL, Ray WA, Strom BL. Medicaid Databases. In: *Pharmacoepidemiology* (4th edn). Strom BL (ed). Wiley, New York, 2005; 281-94
- [26] Gelfand JM, Margolis DJ, Dattani H. The UK General Practice Research Database. In: *Pharmacoepidemiology* (4th edn). Strom BL (ed). Wiley, New York, 2005; 337-46
- [27] Hernán MA. With great data comes great responsibility: Publishing comparative effectiveness research in Epidemiology. *Epidemiology* 2011; 22: 290-1
- [28] Latham J, Murajda L, Forland F, Jansen A. Capacities, practices and perceptions of evidence-based public health in Europe. *Euro Surveill* 2013; 18: pii=20421. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20421>
- [29] Brownson RC, Jamie F, Chiqui JF, Stamatakis KA. Understanding Evidence-Based Public Health Policy. *Am J Public Health* 2009; 99: 1576-83
- [30] Ferrario M, Cesana G, Vanuzzo D, et al. Surveillance of ischaemic heart disease: results from the Italian MONICA populations. *Int J Epidemiol* 2001; 30: S23-9
- [31] Berta P, Seghieri C, Vittadini G. Comparing health outcomes among hospitals: the experience of the Lombardy Region. *Health Care Management Science* 2013; DOI: 10.1007/s10729-013-9227-1
- [32] Bellelli G, Mazzola P, Corsi M, et al. The combined effect of ADL impairment and delay in time from fracture to surgery on 12-month mortality: an observational study in orthogeriatric patients. *J Am Med Dir Assoc* 2012; 13: 664.e9-664.e14
- [33] Bonifazi M, Rossi M, Moja L, et al. Bevacizumab in clinical practice: prescribing appropriateness relative to national indications and safety. *Oncologist* 2012; 17: 117-24
- [34] Bonzini M, Ferrario MM, Bertù L, et al. Temporal trends in ischemic and hemorrhagic strokes in Northern Italy: results from the cardiovascular monitoring unit in Northern Italy population-based register, 1998-2004. *Neuroepidemiology* 2012; 39: 35-42
- [35] Bosetti C, Rosato V, Gallus S, et al. Aspirin and cancer risk: a quantitative review to 2011. *Ann Oncol* 2012; 23: 1403-15
- [36] Bosetti C, Rosato V, Gallus S, La Vecchia C. Aspirin and urologic cancer risk: an update. *Nat Rev Urol* 2012; 9: 102-10
- [37] Bosetti C, Rosato V, Polesel J, et al. Diabetes mellitus and cancer risk in a network of case-control studies. *Nutr Cancer* 2012; 64: 643-51
- [38] Coloma PM, Trifirò G, Schuemie MJ, et al; EU-ADR Consortium. Electronic healthcare databases for active drug safety surveillance: is there enough leverage? *Pharmacoepidemiol Drug Saf* 2012; 21: 611-21
- [39] Corrao G, Nicotra F, Parodi A, et al. External adjustment for unmeasured confounders improved drug-outcome association estimates based on HEALTHCARE utilization data. *J Clin Epidemiol* 2012; 65: 1190-9
- [40] Corrao G, Zambon A, Parodi A, et al. Incidence of cardiovascular events in Italian patients with early discontinuations of antihypertensive, lipid-lowering, and antidiabetic treatments. *Am J Hypertens* 2012; 25: 549-55
- [41] Falcone C, Buzzi MP, Bozzini S, et al, Investigators T. Relationship between s RAGE and eotaxin-3 with CRP in hypertensive patients at high cardiovascular risk. *J Nephrol* 2013; 26: 144-51
- [42] Fattore M, Pelagatti MM, Vittadini G. Inconsistencies of the Pls-pm approach to structural equation models with formative-reflective schemes. *Electron J App Stat Anal* 2012; 5: 334-8, e-ISSN 2070-5948, DOI 10.1285/i20705948v5n3p333
- [43] Giannattasio C, Cairo M, Cesana F, et al. Blood pressure control in Italian essential hypertensives treated by general practitioners. *Am J Hypertens* 2012; 25: 1182-7

- [44] Grassi G, Seravalle G, Brambilla G, et al. Novel antihypertensive therapies: renal sympathetic nerve ablation and carotid baroreceptor stimulation. *Curr Hypertens Rep* 2012; 14: 567-72
- [45] Hu J, La Vecchia C, Augustin LS, et al; the Canadian Cancer Registries Epidemiology Research Group. Glycemic index, glycemic load and cancer risk. *Ann Oncol* 2013; 24: 245-51
- [46] Imberti D, Bianchi C, Zambon A, et al. Venous thromboembolism after major orthopaedic surgery: a population-based cohort study. *Intern Emerg Med* 2012; 7: 243-9
- [47] Ingrassia S, Minotti SC, Vittadini G. Local Statistical Modeling via a Cluster-Weighted Approach with Elliptical Distributions. *Journal of Classification* 2012; 29: 363-401, Springer Verlag DOI 10.1007/s00181-012-9114-3
- [48] Jardine MJ, Hata J, Woodward M, et al; ADVANCE Collaborative Group. Prediction of kidney-related outcomes in patients with type 2 diabetes. *Am J Kidney Dis* 2012; 60: 770-8
- [49] Kane EV, Bernstein L, Bracci PM, et al; for the InterLymph Consortium. Postmenopausal hormone therapy and non-Hodgkin lymphoma: a pooled analysis of InterLymph case-control studies. *Ann Oncol* 2013; 24: 433-41
- [50] Kane EV, Roman E, Becker N, et al; InterLymph Consortium. Menstrual and reproductive factors, and hormonal contraception use: associations with non-Hodgkin lymphoma in a pooled analysis of InterLymph case-control studies. *Ann Oncol* 2012; 23: 2362-74
- [51] La Vecchia C, Bosetti C. Urological cancer: Aspirin and the risk of prostate cancer mortality. *Nat Rev Clin Oncol* 2012; 9: 616-7
- [52] Lapi F, Cipriani F, Caputi AP, et al; on behalf of the Bisphosphonates Efficacy-Safety Tradeoff (BEST) study group. Assessing the risk of osteonecrosis of the jaw due to bisphosphonate therapy in the secondary prevention of osteoporotic fractures. *Osteoporos Int* 2013; 24: 697-705
- [53] Lapi F, Nicotra F, Scotti L, et al. Use of antidepressant serotonergic medications and cardiac valvulopathy: a nested case-control study in the health improvement network (THIN) database. *Br J Clin Pharmacol* 2012; 74: 536-44
- [54] Lovaglio PG, Vittadini G. Multilevel Dimensionality-Reduction Methods. *Statistical Methods & Applications* 2012 - Springer Verlag DOI 10.1007/s10260-012-0215-2, published on-line: 27.9.2012
- [55] Lovaglio PG, Vittadini G. The Balanced Scorecard in Health Care: a Multilevel Latent Variable approach. *Journal of Modelling in Management* 2012; 7: 1746-5664
- [56] Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability, carotid atherosclerosis, and cardiovascular events in the European Lacidipine Study on Atherosclerosis. *Circulation* 2012; 126: 569-78
- [57] Mancia G, Parati G, Bilo G, et al. Ambulatory Blood Pressure Values in the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). *Hypertension* 2012; 60: 1400-6
- [58] Mancia G. Additional drug treatment in resistant hypertension: need for randomized studies. *J Hypertens* 2012; 30: 1514-5
- [59] Mancia G. Reporting blood pressure effects of antihypertensive treatment in scientific papers: are guidelines needed? *J Hypertens* 2012; 30: 1307-9
- [60] Moia M, Mantovani LG, Carpenedo M, et al. Patient preferences and willingness to pay for different options of anticoagulant therapy. *Intern Emerg Med* 2013; 8: 237-43
- [61] Pelucchi C, Chatenoud L, Turati F, et al. Probiotics supplementation during pregnancy or infancy for the prevention of atopic dermatitis: a meta-analysis. *Epidemiology* 2012; 23: 402-14
- [62] Pradelli D, Soranna D, Scotti L, et al. Statins and primary liver cancer: a meta-analysis of observational studies. *Eur J Cancer Prev* 2013; 22: 229-34
- [63] Soranna D, Scotti L, Zambon A, et al. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist* 2012; 17: 813-22
- [64] Torsello A, Bresciani E, Ravelli M, et al. Novel domain-selective ACE-inhibiting activity of synthetic growth hormone secretagogues. *Pharmacol Res* 2012; 66: 317-24
- [65] van Dieren S, Kengne AP, Chalmers J, et al. Effects of blood pressure lowering on cardiovascular outcomes in different cardiovascular risk groups among participants with type 2 diabetes. *Diabetes Res Clin Pract* 2012; 98: 83-90
- [66] Veronesi G, Ferrario MM, Chambless LE, et al. The effect of revascularization procedures on myocardial infarction incidence rates and time trends: the MONICA-Brianza and CAMUNI MI registries in Northern Italy. *Ann Epidemiol* 2012; 22: 547-53
- [67] Vishram JK, Borglykke A, Andreasen AH, et al; On behalf of the MORGAM Project. Impact of Age on the Importance of Systolic and Diastolic Blood Pressures for Stroke Risk: The MOnica, Risk, Genetics, Archiving, and Monograph (MORGAM) Project. *Hypertension* 2012; 60: 1117-23
- [68] Vittadini G, Berta P, Martini G, Callea G. The effect of a law limiting upcoding on hospital admissions: Evidence from Italy. *Empirical Economics on Health Econometrics (special issue)*, Springer Verlag DOI 10.1007/s00181-012-0548-6
- [69] Weber MA, Julius S, Kjeldsen SE, et al. Cardiovascular outcomes in hypertensive patients: comparing single-agent therapy with combination therapy. *J Hypertens* 2012; 30: 2213-22
- [70] Virone MG. EHR and data protection issues in Italy. *Stud Health Technol Inform* 2012; 180: 741-5
- [71] Corrao G. Building reliable evidence from real-world data: methods, cautiousness and recommendations. *Epidemiology Biostatistics and Public Health* 2013; 10(3): e8981. DOI: 10.2427/8981