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Building reliable evidence from real-world data: Needs, methods, cautiousness and recommendations

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A B S T R A C T

National healthcare systems of advanced countries, including Italy, widely agree on the approach whereby public healthcare decisions should be driven by available evidence on effectiveness and safety of therapeutics. It is equally accepted that randomized controlled clinical trials (RCTs), although universally recognised as the most robust "evidence generators", are insufficient for guiding the decision-making process since they are intrinsically unsuited to capture the impact of treatments in routine clinical practice. The complexity of treatments, as well as the demographic and clinical heterogeneity of patients receiving the treatments, and the long period of many treatments, explain the gap between the evidence generated in the controlled, but artificial, setting of RCTs and their current impact in the real world. The so-called pragmatic RCTs, despite guaranteeing greater flexibility compared to conventional trials, are not always able to reduce this gap. This explains the growing interest in the development of methods able to produce evidence on the real-world impact of care pathways (*i.e.*, real-world evidence). Among them, those based on the Electronic Healthcare Records (EHRs), as the databases on the healthcare services of the National Health System provided to beneficiaries, known as Healthcare Utilization Databases (HCU), are becoming established and receiving increasing attention from the scientific community and healthcare decision-makers. We described the research areas in which HCU databases may be particularly useful, jointly with strength, weakness and potential of this approach. It is concluded that HCU data cannot substitute RCTs but they can usefully complement RCT data for adequately supporting healthcare decision-makers.

1. Why are evidence based on clinical trials insufficient?

When making healthcare decisions, patients, physicians and policy makers need unbiased information about the treatment effects on health outcomes, while controlling costs [1]. Randomized clinical trials (RCTs) generate the highest level of evidence on the therapy benefits because they are based on random allocation of participants, so allowing to patients' characteristics to differ between treatment groups only for the effect of chance. In addition, new treatments are compared with placebo or current interventions, which offers information on their absolute and added value.

However, more than 45 years ago, Archibald Cochran stated: "*between measurements based on randomized controlled trials and benefit … in the community there is a gulf which has been much under-estimated.* " [2]. From this claim, we should learn that, although decisions based on RCTs, based on evidence-based guidelines, still offer the best warranty for the decision-making process, expected benefits almost never occur when their results are applied in the real-life. Several reasons explain because this occurs.

First, patients included in RCTs are selected with respect to those who could benefit of the treatment under study for both ethical (*e.g.*, the systematically tendency to excluded the frail individuals, such as children, pregnant women, and elderly people), and statistical reasons (*i.e.*, because the greater the heterogeneity of the sample in study, greater must be the sample size, comorbid patients, as well as those on polypharmacy, are usually excluded). However, in the setting of UK primary medicine, only 3% and 18% of patients with main diagnosis of heart failure and type 2 diabetes mellitus respectively had these conditions alone, on average 5.6 and 6.5 other pathologies coexisted with the main diseases, respectively [3].

Second, guidelines based on RCTs are often disregarded in real-life, because of inappropriateness in prescribing of doctors, and of marginal adherence of patients. For example, according with a recent Italian study in the setting of appropriateness of long-term treatment of chronic obstructive pulmonary disease (COPD), it emerges a relevant gaps between the current clinical practice and the guidelines on integrated COPD management (COPD-GL) from the Italian Ministry of Health, resulted for both medical practice (mean agreement 25%) and health organization (48%) [4]. Furthermore, it has been observed that adherence to guidelines adopted by the Italian Association of Medical Oncology for the treatment of breast, colorectal and lung cancer, is not entirely satisfactory, in particular for stage IIIB lung cancers, and partially for breast and rectal tumours [5,6]. Finally, therapeutic continuity of chronic conditions such as hypertension, dyslipidaemia, diabetes, COPD and osteoporosis (to mention those most prevalent especially in elderly), although not entirely evidence based, is

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Table 1
Adherence and persistence with drug therapies for the primary prevention of cardiovascular outcomes (blood pressure and lipid lowering agents), complications of diabetes (oral hypoglycaemic drugs), respiratory exacerbations (inhaled bronchodilators) and bone fractures (bisphosphonates). Lombardy, 2008–2016.

	Adherence	Persistence
Blood pressure-lowering agents [9]	52%	55%
Lipid-lowering agents [10]	40%	50%
Oral hypoglycaemic drugs [11]	60%	60%
Inhaled long-acting bronchodilators [12]	–	20%
Bisphosphonates [13]	30%	30%

Adherence is the ratio between the cumulative number of days in which the drug therapy was available and the days of the overall follow-up, a measure known as proportion of days covered. Persistence is the continued use of drug therapy during the first year after the patient started treatment without any episode of treatment discontinuation.

nevertheless recommended by the guidelines. Table 1 provides a worrying picture of adherence and persistence with some drug therapies observed in large and unselected cohorts of patients who started the specific therapy for the primary prevention of cardiovascular outcomes (blood pressure and lipid lowering agents), complications of diabetes (oral hypoglycaemic drugs), respiratory exacerbations (inhaled bronchodilators) and bone fractures (bisphosphonates) through a series of studies conducted in Lombardy in the last 10 years [7–11].

Third, because of the great impulse of basic research, in recent years we are witnessing a great acceleration in the development of new drugs based on innovative mechanisms of action addressed to specific molecular targets. The potential benefits of these deliveries, however, risk of not translating into therapeutic availability for the patient due to the slowness of the regulatory process. For this reason, firstly the American Food and Drug Administration (FDA), more recently the European Medicines Agency (EMA) and other regulatory agencies, have revised the rules of the regulatory pathway giving the possibility to the so-called innovative drugs to undergo to a quickened evaluation and conditional marketing authorization [12]. These are the two tools that have revolutionized the regulatory process, and that will most likely result in further regulatory changes to accelerate patient access to medicines for unmet medical needs. In particular, the conditional marketing authorization allows the rapid approval of a drug according to the results of small and brief trials, provided that the drug itself is destined for an unmet medical need, for a disease severely disabling or life-threating, rare disease, or for a public health threat. Although less complete, the available data must however demonstrate that benefits of the drug outweigh its risks, and the applicant will need to be able to provide complete clinical data after authorization within an agreed period.

Finally, the use of the conventional paradigm of evidence-based medicine, and the evidence-based guidelines that are its natural consequence, implies that the healthcare given to the individual diseases is based on the best available evidence. However, this model is not directly applicable for caring complex patients, and more in general is no longer sustainable in the case of chronic diseases [13]. New models for the management of patients with chronic diseases should be characterized by the global and integrated management of the patient's needs, developing and implementing a personalized diagnostic-therapeutic assistance program that ensures the overall response to the needs of the patient as well as the continuity of care and, at the same time, that guarantees the global sustainability of the system thus conceived. This entails the development of a remuneration methods of the route, and the negotiation with the health service providers in the various delivery settings.

Briefly, because of their high internal validity, RCTs still represent the (not replaceable and not renounceable) reference for the choice of individual treatments. However, due to their questionable generalizability that limit their applicability to all patients followed in clinical practice, making both the adherence of the doctors to evidence-based guidelines and of the patients to the doctor's advice questionable, there is a gap between (expected) efficacy according to RCTs evidence and benefits observed in clinical practice (effectiveness). In addition, the acceleration of the regulatory process involves the use on a population scale of innovative treatments whose evidence of efficacy and safety are at least uncertain. Finally, the evaluation of the cares' quality (and of their sustainability) adopted for the management of chronic patients consists of assessing the impact of exposure on the care pathways in term of clinical benefits and economic outcomes, that is the evaluation of the appropriateness and of the risk-benefits and cost-effectiveness profile, through the (planned) observation of real-world clinical practice.

2. Methods for generating real-world evidence

Recognition of the above limitations has favoured the design and conduction of trials that could more appropriately reflect clinical practice. The so-called **pragmatic trials** are becoming very popular for testing clinical hypotheses from patients more similar to those who could benefit from the trial results [14]. However, it is widely acknowledged that pragmatic trials do not substantially reduce the gap between the artificial environment where trial data are collected and real life practice [15]. Furthermore, it should be considered that pragmatic trials require organizational and monetary investments comparable, if not higher, than conventional RCTs. In fact, since the sample of interest is by definition heterogeneous, the sample size required can be very large. Moreover, the organizational issues necessary to manage such studies can also be very expensive [16]. In spite of this, pragmatic RCTs may contribute to address important medical issues. For example, double-blind RCTs in COPD have indicated that inhaled corticosteroids (ICS) combined with a long-acting β2-agonist (LABA) are more effective than the individual components in managing stable COPD, reducing exacerbations and improving lung function and health status [17]. However, double-blind RCTs differ from real life due to the selective eligibility criteria, and because they include participants who are not representative of patients in clinical practice and have much higher adherence [18]. The pragmatic RCT named Salford Lung Study (SLS), evaluated the effectiveness and safety of ICS/LABA combination compared with usual maintenance therapy in a large, real-world population of patients with COPD in conditions of normal care [19].

There is a growth of interest on observational studies that could complement the results of clinical trials with information on how strong and persistent are the effects of healthcare interventions in the real-life conditions. However, it should be stressed that moving from the experimental to the observational approach, respectively implying the planned and the natural allocation to the study treatments, is crucial with respect to the strength of evidence we can obtain. This is very important because, by renouncing random assignment (or at least the choice of the intervention motivated by the objective of the study) implicitly we renounce to the main strength of clinical trials (i.e., randomization). No observational study, by definition, is able to offer this guarantee. For this reason, in his basic text on Evidence-based medicine, David Sackett stated that "… *if you find that study was not randomized, we would suggest that you stop reading and go to the next article* …" [20]!

Within observational investigations, a distinction would be made between prospective primary studies and retrospective secondary ones. **Prospective primary studies** imply in-field collecting data for testing a specific clinical hypothesis, such as the development of a disease following some exposure. These studies usually involve a cohort of subjects who are followed over a long period. Under this point of view, prospective primary studies differ from (both pragmatic and conventional) clinical trials just because they do not imply random assignment