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POSITION PAPER

Towards the rational use of Healthcare Utilization Databases for generating real-world evidence: new challenges and proposals

A position paper from the
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The decision-making context leading to the approval of care devices has by now reached maturity. The national healthcare systems of advanced countries, including Italy, widely agree on the approach whereby public healthcare decisions should be driven by available evidence of the 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 inadequate for guiding the decision-making process in that they are intrinsically unsuited to capture the impact of treatments in routine clinical practice. Complexity of treatment regimens, demographic and clinical heterogeneity of patients receiving treatments, and the long time frame of many treatments, explain the gap between the evidence generated in the controlled, but artificial, setting of RCTs and its actual impact in the real world [1]. So-called pragmatic RCTs, while guaranteeing greater flexibility compared to conventional trials [2], are not always able to reduce this gap [3].

This explains the growing interest in the development of methods able to produce evidence on the real-world impact of care pathways [4]. Among them, those that use electronic databases of healthcare services provided to beneficiaries of the National Health System (NHS), known as Healthcare Utilization Databases (HUDs), are becoming established and receiving increasing attention from the scientific community and healthcare decision-makers [5].

This attention is justified by at least five reasons: 1) the ready availability of data reduces the time and costs of research; 2) the inclusion of very large populations (e.g., beneficiaries of NHS) allows discovery of even extremely rare adverse events; 3) the availability of large temporal series makes it possible to study the long-term outcomes of chronic treatments;

4) the virtually unselected nature of the target population allows for results that can be generalized to the real-world of routine clinical practice; 5) the possibility of keeping track of the extent and manner in which healthcare services are prescribed by physicians and used by patients, of evaluating whether treatments succeed in preventing the outcomes they are meant to avoid, and of documenting the economic sustainability of medical interventions, explain the enormous potential of HUDs as a tool to support decisions.

These potential benefits imply an analysis of the entire history of diagnostic and therapeutic pathways of each individual NHS beneficiary [6]. This suggests that the topic we are dealing with should, to all intents and purposes, be considered within the context of clinical research and its implications for public health. The general objective is still to obtain evidence that completes (and not competes with) experimental evidence. Pressures for using HUDs for market research on single products should be viewed with suspicion, as it has nothing to do with the decision-making needs of the public healthcare sector, and do not use clinical research methods.

There are, however, serious reasons to justify considerable scepticism towards the ability of HUDs to adapt to the requirements of clinical research. This scepticism stems from the fact that HUDs are designed and maintained mainly for the purposes of managing claims for reimbursements for healthcare services, as well as of monitoring the rational use of healthcare. Clinical research is, at the most, a secondary use of HUDs. This justifies the following two considerations.

The first refers to the quality of HUDs. It should, however, be noted that a medical service eligible for NHS reimbursement, which has effectively been provided to an individual, is unlikely to be omitted by the system since this would mean that the service provider would receive no reimbursement. On the other hand, the possibility that an undelivered service is recorded should be considered an exception as this would have legal implications [7]. As a result, the quality of data, although it requires careful checking and monitoring, does not justify the scepticism [8].

The second consideration refers to the completeness of the data relating to each service, including the reasons justifying its provision. If, as recalled above, HUDs serve to document the delivery of a service, there is no reason why they should contain information such as the medical condition warranting the service, its severity/stage, concurrent diseases, prescribed drug dosages, body mass index, blood pressure, laboratory test findings, lifestyle, etc… The most serious reason for scepticism is therefore the lack of data rather that their quality. Clinical research framework based on HUDs is often obliged to make gross approximations (e.g., on prescribed drug dosages) and accept assumptions that cannot be directly verified (e.g., on the role of unmeasured variables in explaining the observed association). The real challenge in the use of HUDs for generating credible evidence to support decisions, lies in our ability to tackle these vulnerabilities by adopting adequate tools [9]. In recent years, however, methodological research has made extraordinary progress with the development of methods, algorithms, and designs that overcome, or at least rationally take into account, the pitfalls of observational research, especially when based on HUDs [10-13]. For this reason we believe that the real challenge is not technology or our ability to devise tools for storing, updating and analysing huge amounts of data; rather, it is related to the scientific method itself and our ability to develop robust observational plans and adequate methods of analysis capable of taking into account the complexity of phenomena and generating reliable evidence.

These considerations should not be taken as an attempt to shift the debate from the realm of healthcare management - viewed as too complex to adapt to the rigour of the scientific method - to that of typically academic scientific speculation. Monitoring and assessing the effectiveness of delivered healthcare services and evaluating the appropriateness and quality

of care are activities that unfold within two frames of reference. The first is more pragmatic and relates to the NHS's purpose of protecting citizens' health through its territorial branches (Regions first of all) and institutional agencies (e.g. the Italian Medicines Agency, AIFA).

The second is more speculative and relates to the production of generalizable evidence (for example) on care pathways ensuring the highest effectiveness at sustainable costs. Pragmatism and speculation, however, work towards a common goal: the generation of reliable evidence able to inform choices (the decision-maker's perspective) and guide research (the researcher's perspective). Regardless of the perspective taken, however, we cannot disregard the method used to generate the evidence. And it is precisely the method, a requirement of decision-makers and researchers alike, should act as a bridge between pragmatism and speculation.
HUDs, and more in general any clinical or administrative retrospective database constructed for purposes other than exploring a scientific query, have an important peculiarity. Under torture, but even when the researcher querying them is acting in all good faith, they are instruments that can generate results that point in all directions. This is disconcerting and causes considerable distrust towards their use. The following considerations and proposals may help to overcome this.

The first consideration is that one should demand that the rules according to which the study will be conducted (rationale, objectives, sources, analyses) should be defined in advance and explicitly stated in a document, the study protocol, that must be submitted to an expert committee for assessment [14]. In other terms, the principles of good clinical research practice, which are universally accepted and strictly regulated in drug and medical device testing, should be adapted to the context at hand [15]. Adapted, not strictly applied, since the context is substantially different. Here, we are dealing with non-interventional studies that imply no additional risk for the patients' health, where the medical intervention is an integral part of clinical practice and stems from treatment decisions that are independent of the study. Besides, the data are already available (retrospective, according to current terminology), and involves patients that cannot objectively be tracked down at the time the study is started. In Italy, this type of study is regulated by the *"Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci"* (Guidelines for the classification and conduction of observational studies on drugs) [16]. Briefly, the rules state that the start of an observational study is subject to formal approval by an Ethics Committee (EC) only if the study is a prospective cohort design, that is, if patients are included based on their taking a certain drug and followed up over time to evaluate the outcomes. By contrast, for retrospective observational studies, such as those addressed in this paper, notification of the EC is sufficient.

The question we should be asking ourselves is: do the above characteristics of such studies justify the regulatory relaxation towards HUD-based studies? In our opinion, only in part: although these studies do not involve additional risks for the patient and do not require the patient's consent, they are nonetheless able to produce results/evidence that affect clinical practice and guide decisions. Setting up a national registry of observational studies aims to improve the transparency of research, but who duty is to ascertain that the research is being conducted according to the good practice rules of observational research? Often not the EC's, given that regulations only provide for its notification, not approval. On the other hand, we are not sure that the EC is the most suitable body for the context being considered. For two reasons: firstly, because observational research on medical services is not limited to drugs and medical devices, but extends more in general to preventative, diagnostic, therapeutic and rehabilitation pathways experienced by the NHS users; secondly, because, whereas the expertise for judging the methodological aspects of experimental research is widespread, consolidated and solid, the specific sector we are discussing is still relatively unexplored for many clinical investigators.

The second consideration is the acknowledgement that the Regions are effectively the

producers of HUDs, as well as the bodies responsible for handling the sensitive data they contain and, as such, they claim ownership over their HUDs and regulate their use. The recent decision no. X / 2017 of the Lombardy Region approved by the Regional Council on 1st July 2014 goes in this direction by defining the rules for access to the Lombardy Region's DataWareHouse data by external bodies (*"Regole per l'accesso ai dati del DataWareHouse di Regione Lombardia da parte di Enti esterni"*) [17]. The rationale is very sound: having acknowledged that the Region, in planning, managing, controlling and assessing healthcare, needs to valorise the information content of HUDs, in a perspective of scale economy it makes its data available to external accredited bodies, provided that data are used to fulfil the Region's planning needs. The main requirement for accreditation of an external body is that it should have already developed, and published in indexed journals, models for the integrated use of HUDs for healthcare monitoring. Once accredited, a body may present one or more projects falling within the research areas established yearly by the Region, by submitting applications and lists the data required. While emphasizing once again our basic appreciation of the initiative and in the hope that other Regions will follow the example of Lombardy, we nonetheless believe that applications should include a detailed protocol that defines in advance the rules with which the study will be conducted. Our proposal is to set up a single Regional Evaluation Committee (REC), made up of professionals external to the Regional Administration and having documented relevant expertise, to be put in charge of reviewing protocols for assessing their methodological soundness. We do not think the REC should express binding opinions, but rather it should have a consultative role for the Regional Healthcare Authority. We also believe that REC competences should extend not only to the regional administrative databases but also to other secondary data sources that cover the regional population (e.g., disease registries, electronic general practitioner networks, clinical databases, etc…). The systematic review of protocols would place the REC in a position to perceive the training needs of regional research groups and to promote training courses, thereby establishing a virtuous pathway for enhancing the quality of research. Nor should we neglect the fact that the creation of RECs would relieve the EC from a duty that is overly cumbersome and fragmentary across the territory.

The third consideration stems from the need to guarantee a wider (multiregional) overview of healthcare in addition to a regional view. It is in everyone's interest to enable the Ministry of Health, government bodies [such as the Italian Medicines Agency (AIFA) and the National Agency for Regional Health Services (Age.Na.S)], public research centres [such as Universities and the National Research Council (CNR)], each for its own purposes, to make use of the huge amounts of information contained in regional HUDs. Common sense helps to reject the idea of setting up a national HUD to include and aggregate the single regional databases. Rather, we should prepare to provide the single Regions with a common, rigorous, standardized and uniform methodology [18], so as to produce reliable indicators that lend themselves to inter-regional comparisons of delivered healthcare services (primary concern of the Ministry of Health) and to generate evidence that can be used to inform choices (primary concern of the Regions). This implies the need for an institutional coordination of RECs whose mission would be to standardize the criteria for HUD use, develop good practice guidelines for observational studies with secondary data, support the Regions with adequate competences and infrastructures, and monitor regional activities in this context.

The final consideration is a more general "challenge in a challenge" as it refers to the dramatic lack of public research funding which has characterized Europe during the recent crisis, but which continues to strangle our country in particular [19]. Since we exclude any increase in funding within a reasonable time frame, the only way to restore competitiveness is to create the conditions for an alliance between the public sector and the business community - without, however, forgetting that the two parties have different goals. In this context, Academy may play a precious role. The European Community, in launching a new way of supporting and valorising scientific advancement with its *Horizon 2020* programme [20]

has identified excellence in science, industrial leadership and societal challenges in health and wellbeing as the three pillars on which progress should be based. Encouraging initiatives calling for cooperation between NHS, Academy and enterprise means both preparing the ground for improving the quality and competitiveness of research by recognising that research itself is a driver for development, and generating evidence capable of guiding decisions to ensure effective, equitable and sustainable care. To this end, we may need to promote new lines of research, unprecedented opportunities providing a common ground between different needs.

In conclusion, the potential of HUDs is enormous. The possibility of developing a system which, based on the past experience of NHS users, is capable of informing choices on the best way to treat patients in the future [21], is a challenge we have to take. To do so, we need to prepare by investing on the quality of research and the training of professionals willing to face new challenges, by setting up adequate infrastructures aiming to make a scientifically sound use of each Region's healthcare information assets, by harmonizing ongoing initiatives including those providing HUD access to public bodies external to regional administrations, and finally by negotiating the terms of the cooperation between NHS, Academy and enterprise.

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