Recenti Prog Med 2021; 112: 97-99

From snapshots to a movie. Challenging the patterns of academic research

FRANCESCO PERRONE[1]

[1]Unità Sperimentazioni Cliniche, Istituto Nazionale Tumori di Napoli, IRCCS Fondazione Pascale, Napoli.

Pervenuto su invito l'8 febbraio 2021.

Summary. Academic research should foster study projects focused on the efficacy of therapeutic pathways (patient-journey studies) instead of just individual drugs. The research for registration purposes gives us snapshots, thanks to which the new drugs arrive on the market. What is before the photo is not necessarily clear; for example, the characteristics of the patient population, which often differ between the trial and clinical practice that could begin years later. As it is not clear what there is after the photo; for example, the subsequent treatments which also change over time. Indeed, the time frame following the photo is often deliberately obscured by using surrogate endpoints that overestimate advantages. Regulatory agencies are called upon to decide on registration and reimbursement despite being essentially unable to fully understand the value, positioning and economic consequences of new drugs. This is the field in which independent research must try its hand in the coming years. By designing studies on therapeutic pathways, which assess the effectiveness of therapeutic sequences by looking at the entire patient-journey and not at the efficacy of individual drugs. Something like going from a series of snapshots to a movie.

Dalle istantanee al film. Sfidare i modelli di ricerca accademica.

Riassunto. La ricerca accademica dovrebbe promuovere progetti di studio incentrati sull'efficacia dei percorsi terapeutici (studi sul percorso del paziente) invece che sui singoli farmaci. La ricerca ai fini regolatori ci fornisce delle istantanee, grazie alle quali arrivano sul mercato i nuovi farmaci. Tutto quello che precede la foto non è sempre chiaro; pensiamo per esempio alle caratteristiche della popolazione di pazienti, che spesso differiscono tra la sperimentazione e la pratica. Allo stesso modo, non è chiaro cosa ci sia dopo la foto: per esempio il percorso terapeutico successivo al trattamento studiato. Spesso, infatti, il lasso di tempo che segue la foto viene volutamente messo in secondo piano utilizzando endpoint surrogati che sovrastimano i vantaggi. Le agenzie regolatorie sono chiamate a decidere in merito alla registrazione e al rimborso nonostante non siano del tutto in grado di comprendere appieno il valore, il posizionamento e le conseguenze economiche dei nuovi farmaci. Questo è il campo in cui la ricerca indipendente dovrà mettere se stessa alla prova nei prossimi anni. Progettando studi sui percorsi terapeutici, che valutino l'efficacia della cura guardando all'intero percorso del paziente e non all'efficacia dei singoli farmaci. Qualcosa di simile al passare da una serie di istantanee a un film.

At the end of 2004, the non-profit decree marked an ontological watershed for academic research in Italy. After that decree, academic research formally began to exist. It will be said: in fact, it already existed before. Yes, that's right, but let's talk about *before*.

Long before, the rules for clinical research were almost non-existent except for the need to ensure that no ethical havoc was done; and therefore the Helsinki declaration and other similar things were enough. It was a time when drugs were cheap, no one was worried about the appropriateness of prescribing, and few knew the drug labels in detail.

On the contrary, *shortly before* 2004, the rules of clinical trials (called "good clinical practice" - GCP, and the name shows that some confusion existed) had been written because the economic value and the price of drugs were growing, the role of the pharmaceutical industry as the main sponsor of the studies was growing, and the attention to appropriateness, which meant (and still means in a too minimalist view) prescription literally consistent with the label, was growing as well. Furthermore, a European Directive of 2001 implemented in Italy with a decree in 2003, frightened everyone in Europe, because it not only certified the obligation to comply with the GCP but also introduced a sanctioning system that could have brought academic research to its knees[1-3]. In the presence of these rules and before the non-profit decree, academic research had become an activity done almost in secret, with the risk that at any moment someone could accuse us of doing something against the rules or not sufficiently in tune with them. Undoubtedly, if an evil genius had wanted to verify in a quirky way what we had done up to that day, he would have found more than one thing to complain about.

Therefore, the non-profit decree of December 2004 represents the legal birth certificate of academic clinical trials in Italy and it cannot be ignored.

16 years later, it's worth trying to question ourselves about the use we have made of it. Because when the new European directive comes into force,

maybe by the end of 2021, that decree will go into obsolescence; and because we were the recipients of that decree. We scientific institutes, we universities, we hospitals. Not others. It was our right to do clinical research that was recognized and imposed in the system of rules that, on the contrary, could apparently be interpreted only by pharmaceutical companies. And not only did we exist, but we were also identified as a protected category, which were guaranteed special care, and small or big operational advantages.

The title of the Italian decree, it is worth remembering, sounds like «General prescriptions relating to the execution of clinical trials of medicines, with particular reference to those for improving clinical practice, as an integral part of health care» (GU General Series n. 43 of 22-02-2005). Did we use it right? Did we take advantage of the benefits we were given? Have we "improved clinical practice"?

If we critically reviewed the clinical trials done in the name of that decree, I am sure we would find pearls, particularly (as regards oncology) among the studies funded by calls of the Italian Drug Agency (AIFA); but I also fear that pearls do not represent either the totality or the majority of the things we have done.

Placing in therapy is a challenge

In oncology, for example, independent research has not sufficiently addressed the problem of therapeutic sequences and the best strategic positioning (so called place in therapy) of the numerous new drugs that are becoming available in recent years.

A clear example of this is hepatocellular carcinoma, the subject of the review by Celsa et al., published in this issue of the journal[4]. After many years of only one drug being available (since 2008), the options for medical therapy for patients with tumor not eligible for a locoregional treatment and with compensated liver function have recently begun to increase. Today, in Italy, there are four registered and reimbursed drugs. Of these, only one was compared versus the previous standard in a first-line non-inferiority study, while all the others were compared versus placebo and never with each other, in the second line of treatment. It follows, today, the possibility of articulating different sequences, even up to three therapeutic lines, on the basis of limited evidence, never coming from direct head-to-head comparisons. In addition, in Italy too the first line approval of two monoclonal antibodies will be discussed shortly, because their combination, by stimulating the immune response and inhibiting angiogenesis, proved to be more effective than the standard in a head-to-head comparison. How will the new therapeutic algorithm be articulated? Surely, one more option, with a treatment that significantly prolongs survival over the previous standard, is a value. But what do we know about the treatments to be done afterwards, for those patients who will still suffer a progression of the disease? Little, very little, because we have no studies on therapeutic sequences; common clinical sense will be the only precious instrument to decide, lacking experimental evidence. And what will happen when new treatments arrive once again with no head-to-head comparison? Even more, we will not have clear ideas, and we might not be able to make the best use of treatment options available for future patients.

Well, in my opinion, academic research should respond to problems of this type (and many other similar ones that are emerging in oncology), thinking about study projects focused on the efficacy of therapeutic pathways (patient-journey studies) instead of just individual drugs. The research for registration purposes gives us snapshots, thanks to which the new drugs arrive on the market. What is before the photo is not necessarily clear; for example, the characteristics of the patient population, which often differ between the trial and clinical practice that could begin years later. As it is not clear what there is after the photo; for example, the subsequent treatments which also change over time. Indeed, the time frame following the photo is often deliberately obscured by using surrogate endpoints that overestimate advantages, avoiding the natural dilution resulting from subsequent treatments. Building a therapeutic path based on some snapshots can be simple if the possibilities are few, one or two drugs; but it becomes complicated if (fortunately) the options increase in number. It follows that the guidelines of scientific societies are increasingly developed on weak evidence, and that regulatory agencies are called upon to decide on registration and reimbursement despite being essentially unable to fully understand the value, positioning and economic consequences of new drugs (always obviously very expensive).

Studying therapeutic pathways

I believe this is the field in which independent research must try its hand in the coming years. By designing studies on therapeutic pathways, which assess the effectiveness of therapeutic sequences by looking at the entire patient-journey and not at the efficacy of individual drugs. Something like going from a series of snapshots to a movie. A movie where, at each decision point, it is possible to choose between the treatments available in the real world (possibly motivating the reason for the choice) or to propose a randomized clinical trial, where the scientific community first, then the patient and the doctor, agree that an uncertainty exists. Such a movie would allow for the optimization of existing treatments, verifying which sequences are the best and strengthening the evidence underlying the algorithms to be recommended in clinical practice. It would be possible to overcome the dualism between real-world evidence and prospective randomized trials, improving the quality of the former and the generalizability of the latter. Finally, it would make it possible to build solid

contexts for the analysis of the economic impact of new drugs, too often based on very little data and many theoretical models.

As mentioned previously, this is probably the moment in which the strategy of academic research in Italy and in the world must be re-discussed. And just as at the beginning of the century we asked for academic research to be recognized and we were proactive in a season of great harmony with the institutions, even today, and perhaps even stronger due to the dramatic experience of the coronavirus pandemia, we have to propose new models to enhance and update the role of academic research, on which the improvement of clinical practice, which is the ultimate goal of our work as doctors and researchers, necessarily continues to depend.

Conflict of interests: FP reports, in the last 4 years, educational activity or advisory board from: Bayer, Janssen Cilag, Pierre Fabre, AstraZeneca, Celgene, Incyte, Sandoz, Bristol Myers Squibb, Ipsen, Eli Lilly; Cerismas, SIFO, ALTEMS, Humanitas, SMA, UniMoRe, Bocconi, AIOT, Campus Biomedico.

Bibliografia

1. Habeck M. Gloomy prospects for European cancer research. Lancet Oncol 2003; 4: 66.
2. Watson R. EU legislation threatens clinical trials. BMJ 2003; 326: 1348.
3. Wilkinson E. European Directive could halt trials in UK. Lancet Oncol 2003; 4: 456.
4. Celsa C, Giuffrida P, Stornello C, et al. Systemic therapies for hepathocellular carcinoma: the present and the future. Recenti Prog Med 2021; 112: 110-6.

Corresponding author:
Dr. Francesco Perrone
Unità Sperimentazioni Cliniche
Istituto Nazionale Tumori
IRCCS Fondazione Pascale
Via Mariano Semmola
80131 Napoli
E-mail: f.perrone@istitutotumori.na.it