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GIENS WORKSHOPS 2021/HEALTH TECHNOLOGIES

Health crisis: What opportunities for clinical drug research?☆

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Summary The COVID-19 pandemic led to the deployment of an unprecedented academic and industrial research effort, the sometimes redundant nature of which is regrettable, as is the lack of both national and international management. However, it must be noted that during this crisis, regulatory procedures were adapted and certain obstacles in the organisation of clinical research were partly removed to contribute to the deployment of trials as close as possible to patients and to facilitate monitoring and control procedures. The digitisation of certain processes and the decentralisation of certain activities were implemented under the cover of a mobilisation of the authorities and all institutional, academic and industrial players. While in the UK, the optimisation of resources through a single platform trial has made it possible to demonstrate or invalidate the efficacy of many treatments, in France the health crisis has highlighted the fragility of the organisation of clinical research, in particular a lack of coordination and funding, difficulties in implementing studies and a certain reluctance to share data. However, the crisis has also revealed the adaptability of the various stakeholders and has led to the improvement of several processes useful for the deployment of therapeutic innovation. Let us hope that the lessons learned during this crisis will allow for greater efficiency in the event of a new pandemic and, above all, that the progress made will continue to apply to all future clinical research activities.

Abbreviations

ANR	National Research Agency
ANRS-MIE	ANRS - Emerging Infectious Diseases
ANSM	National Agency for the Safety of Medicines and Health Products
AP-HP	Assistance Publique-Hôpitaux de Paris
BPI	Public Investment Bank
CAPNET	ad hoc National Steering Committee for Therapeutic Trials and Other Research on COVID-19
CHU	centre hospitalier universitaire
CLCC	Centre de lutte contre le cancer
CNIL	Commission nationale de l'informatique et des libertés
COVID	coronavirus disease
CPP	Committee for the Protection of Individuals
CRO	Clinical Research Organization
DRCI	Clinical Research and Innovation Department
FCRIN	French Clinical Research Investigation Network
GCP	good clinical practice
IGESR	General Inspectorate of Education, Sport and Research
LEEM	The French pharmaceutical companies
MESRI	Ministry of Higher Education, Research and Innovation
MSS	Ministry of Health and Solidarity
PHRC	Hospital Clinical Research Programme
PIA	programme d'investissements d'avenir
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SFPT	French Society of Pharmacology and Therapeutics
SIGREC	Information and Management System for Research and Clinical Trials
SNDS	National Health Data System
WHO	World Health Organization

Introduction

By the end of December 2019, first cases of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection were reported and what started as an epidemic quickly became a global pandemic. Today, more than 18 months later, nearly 245 million people have been infected and nearly 5 million have died. Beyond the health impact, this crisis, unprecedented in the last fifty years, has caused major disruption throughout the world, requiring unprecedented containment measures with undeniable societal and social consequences that are still difficult to measure to this day. At the same time, in a scientific and medical context that has no comparison with that of major historical crises such as the Spanish flu pandemic, the genetic sequence of the virus was determined as early as January 2020, opening the way to numerous research projects, particularly therapeutic ones. As far as drug research is concerned, this crisis was, as we shall detail, a revelation of the strengths and weaknesses of medical research, and even of our societies as a whole. All these elements require a certain form of inventory and the elaboration of some proposals or recommendations so that these errors or, on the contrary, the agility of certain solutions can be better taken into account in the event of a possible future crisis. Although preclinical and even basic research have been the subject of similar difficulties, we have focused the discussions of our roundtable on clinical drug research, excluding, however, pharmacoepidemiology and pharmacovigilance approaches.

An unprecedented research effort

Numerous clinical trials that are sometimes redundant or even questionable

From January 2020 to June 2021, on a global scale, more than 1,800 therapeutic trials were initiated and declared on the clinicaltrial.gov website, which lists the majority of the research in progress. This unprecedented level of activity over such a short period of time and for a single disease certainly reflects the significant responsiveness of the various stakeholders, particularly academics, and the ability to rapidly organize clinical research activity on drugs. However, several pitfalls should be highlighted. Firstly, the coordination of these activities at national and international levels, both in terms of science and resource mobilisation, was particularly limited, as was highlighted in a report by the General Inspectorate of Education, Sport and Research (IGESR) published in June 2021 [1]. The second observation is the significant redundancy of research leading, for example, to the evaluation of hydroxychloroquine in more than 250 trials, or that of ivermectin in nearly 100 studies [2]. It must be noted that, in most cases, these trials consisted of a repositioning of old drugs on theoretical bases that were not always very well argued from a pharmacological point of view, and that they regularly disregarded the necessary preclinical exploration. Subsequent preclinical evaluation has shown the ineptness of such a repositioning [3,4]. Finally, we must emphasise the use of methodological approaches that are sometimes questionable, or sometimes unjustifiable, even in the context of a health emergency [5].

Behind the redundancy of the tests, the methodological issues

If in an emergency, and faced with patients in a serious condition, it could be legitimate to try innovative therapeutic approaches on the basis of a few theoretical elements, the long-term repetition of methodologically questionable studies, particularly in the absence of a comparison group and relevant judgment criteria, cannot be justified [5]. The main risk in this context was the adoption of non-validated treatments and their possible widespread use even though the level of evidence could not justify it. The example of hydroxychloroquine, which appears totally caricatural in this context, is well known.

However, other examples, such as remdesivir, can be used to demonstrate the value of using a sound methodology. In an initial open-label compassionate study published online in the *New England Journal of Medicine* in April 2020, it was reported that 68% of patients treated with this drug benefited from it [6]. However, subsequent studies conducted under better methodological conditions, in particular with a comparator, or even in a double-blind, placebo-controlled study, showed only a discrete effect of this molecule, i.e. a reduction of at best a few days in the recovery time without any effect on mortality [7,8]. These observations remind us of the importance of implementing, even in emergency situations, methodologically sound therapeutic trials, which are the only way to demonstrate the benefit of a treatment.

This health crisis was also an opportunity to deploy specific methodologies on a large scale, in particular so-called platform trials. These original trial designs, used in particular in oncology, allow the evaluation of several treatments simultaneously or over time, with the different arms interrupted or added depending on the intermediate analyses [9]. In the context of coronavirus disease (COVID), we can cite the deployment of the World Health Organization (WHO) SOLIDARITY protocol, a protocol implemented in France and Europe in the DisCoVeRy study [8]. We should also mention the RECOVERY protocol developed with great success in Great Britain, a protocol that has in particular made it possible to demonstrate quite rapidly the benefit of dexamethasone treatment on the survival of patients hospitalized for COVID-19 [10]. These trials, which are currently ongoing, have the advantage of being able to adapt the evaluation of treatments to the evolution of knowledge. However, their dissemination requires particular attention to certain methodological aspects such as the choice and possible evolution of the comparator group and the statistical tools used to analyse the results [9].

Acculturation of the competent authorities in the field of drug evaluation will undoubtedly also be necessary so that these clinical trial platforms can eventually allow the marketing of new treatments.

Recommendations

The roundtable discussions resulted in two recommendations on these topics:

- set up a national coordination tool in the event of a health crisis: such a tool would be designed to steer research activities (from the most basic to clinical applications)

and to optimize access to resources. It is desirable that a regional version be discussed or, at the very least, that the national body interact directly with local players for short, medium and long-term planning of research activities. This role, which will probably be dedicated to the ANRS — Emerging Infectious Diseases (ANRS-MIE), should also include actors or representatives from the private sector;
- refining methodological approaches to clinical research in times of health crisis: this includes taking into account the advantages and disadvantages of platform trials or new clinical trial designs, acculturating the various actors to these methodologies and preserving small-scale clinical trials for the purpose of ''proof of concept'' before conducting large-scale trials.

From national steering to the deployment of studies in local medicine

Acceleration of authorization processes

The rapid growth of many clinical trials in France has been greatly facilitated by significant changes in the regulatory authorization process without compromising safety. Thus, from the beginning of the health crisis, a short circuit dedicated to clinical studies on COVID was set up by the Ministry of Health and Solidarity (MSS) so that projects would receive the opinion of a Committee for the Protection of Individuals (CPP) within approximately 15 days or less. The French National Agency for the Safety of Medicines (ANSM) adapted its ''Fast-Track'' procedures to respond to requests from academic and industrial sponsors within a very short timeframe. Such procedures, inconceivable in normal times, have enabled the authorisation of a large number of studies and clinical trials over a period of a few months. Admittedly, the acceleration of the authorisation process undoubtedly owes a great deal to the fact that clinical research in other fields was partly at a standstill, but this nevertheless demonstrates that when the means implemented are adapted to the demand, the processes usually considered too long and complex can be optimised without making any concessions in terms of quality and safety. During the crisis, the limit of this system was nevertheless reached when the number of new projects exceeded the capacity to process files, requiring the implementation of a slightly more restrictive prioritisation process.

Progressive implementation of a prioritization system

Although national coordination was initially lacking, a National Ad-hoc Steering Committee for Therapeutic Trials and other research on COVID-19 (CAPNET) was set up in the last quarter of 2020 to better coordinate research and introduce a regulatory mechanism to prioritize studies with a presumed high potential. This regulation was based on the definition, by the scientific council of REACTing (Inserm's multidisciplinary consortium in the field of emerging infectious diseases pre-existing the health crisis), of evolving prioritization criteria and the attribution by CAPNET of a ''national research priority'' label to a limited number of studies based on these recommendations.

This ''national research priority'' label allowed exclusive access to an accelerated evaluation procedure for the regulatory authorisation file, a specific valuation of inclusions via the Research and Clinical Trials Management Information System (SIGREC) as well as possible access to institutional funding. CAPNET was initially composed of representatives of the central administration of the interministerial research unit, institutional representatives of health research and academic clinical trial sponsors (Conference of University Hospital Directors), representatives of the researcher-clinician and investigator communities (Conference of CME Presidents), representatives of medical training and research units (Conference of Medical School Deans) and user representatives. Representatives of REACTing, ANSM and CPP also sat on the committee as contributors, without decision-making power, in order to inform CAPNET about the trials in progress. The presence of the ANSM and the CPPs on this committee did not condition the opinion given by these bodies in their respective fields of competence. The setting up of CAPNET marked a turning point in the implementation of new studies or new clinical trials relating to COVID, notably limiting access to an accelerated authorisation process. However, among the points that have been debated, we can list the question of the prerogatives of this committee and its operating methods as well as a lack of transparency on the criteria used for prioritising projects and their possible funding.

Research in ambulatory and primary care medicine needs to be consolidated

At the local medical level, outside of hospitals or hospital centres, university hospitals (*centre hospitalier universitaire* [CHU]), Cancer Centres (*Centre de lutte contre le cancer* [CLCC]), etc., which are involved in numerous research projects, the implementation of clinical research involving primary care workers has been more difficult. This is mainly due to the fact that, even outside of any health crisis, research involving primary care actors remains, for various reasons, the poor relation of clinical research in France. It would undoubtedly be interesting in the long term to review and improve the links between the city and the hospital on these subjects. The example of the COVERAGE project set up by the Bordeaux University Hospital is undoubtedly quite emblematic of this subject, while illustrating perfectly the practical difficulties of implementing large-scale ambulatory therapeutic research. Similarly, the impossibility of finding concrete solutions to involve general practitioners in the evaluation of vaccines, despite numerous discussions within COVIREIVAC, the platform set up to develop COVID vaccine research in France, is again symptomatic [11]. The development of primary care research therefore remains a major challenge for our country. The development of mobile clinical research units or the support of health centres could be decisive elements. At the very least, the research training of future primary care workers remains a fundamental issue so that, in the event of a subsequent health crisis, the deployment of a local research activity can be effective. The opening of dedicated calls ,

such as the ReSP-Ir call for projects open in the summer of 2021, could undoubtedly contribute to the development of these research activities.

Recommendations

The topics developed above have led to three additional recommendations:

- clarify the prerogatives, operating procedures and prioritization criteria of CAPNET, which must remain an exceptional crisis measure;
- capitalise on the fluidity of regulatory processes beyond the health crisis for all research topics. This implies an increase in the resources of the CPPs and the ANSM, while ensuring that the implementation of the European regulation on clinical trials does not hinder this approach;
- establish the necessary environment for the involvement of primary care providers, including private practitioners, in ambulatory clinical research. This implies reinforcing the training of doctors, changing the regulations on several aspects (management of centres, treatments, etc.) and above all strengthening the links between private practice and hospital medicine.

Digitization and decentralization of clinical research

Rapid adaptations to containment measures

The health crisis and the generalized lockdown of March 2020 made it necessary to rapidly adapt the deployment and monitoring of research. A number of research projects in progress, particularly those not involving drug trials, were therefore interrupted. On the other hand, every effort was made to maintain the follow-up and treatment of patients previously included in therapeutic trials, and in some fields of research, such as oncology, to maintain the possibility of new inclusions at all costs. Thus, remote monitoring methods were sometimes set up and, above all, after consultation between investigators and sponsors, it was sometimes possible to administer treatments at home provided that a secure circuit has been set up. On the other hand, when it was not possible to welcome personnel from outside the hospital, procedures for adapting the monitoring were put in place through, for example, the reciprocal delegation of the monitoring activity between academic sponsors or the implementation of remote monitoring procedures. In this context, the CNIL published in April 2021, recommendations on the provisional implementation of this remote activity [12]. The pandemic has thus made it possible to remove, at least temporarily, a certain number of blockages with a catalytic effect on several topics that had remained on standby for many years.

Remaining obstacles

Despite some progress, not all problems have been definitively resolved. Indeed, as far as the implementation of remote procedures is concerned, whether for consent, delivery of treatments, patient follow-up or monitoring, the regulations and their interpretation remain restrictive or even inappropriate. Moreover, we can underline the problem of responsibility that this may raise for the investigator in charge of a patient. In addition to these regulatory problems, as the number of digital tools used in therapeutic trials increases, the digital divide, resulting from inequality of territorial access to the Internet, to which is sometimes added the lack of equipment, is likely to widen the divide in access to therapeutic innovation if such media become unavoidable. In this context, it is important that the various partners in therapeutic research (academic stakeholders, industrialists, institutions, etc.) work together to make progress on these issues, which is an essential step in promoting early access to therapeutic innovation for patients.

Recommendations

In this context, the roundtable was able to identify several additional recommendations:

- to develop the legal and regulatory framework in a sustainable manner on the subject of remote monitoring in particular, taking into account possible technological developments over time and integrating future constraints possibly linked to the European regulation on drug trials;
- develop and have technical solutions adapted to remote monitoring by integrating the problem of interoperability (which some private operators are already capable of managing), by proposing, if necessary, mirror server systems with access restricted to the necessary data only, or by capitalising on the many health data warehouses that are currently being set up in a number of health establishments;
- to refine the regulatory framework of good clinical practice (GCP) on the issue of investigator responsibility versus the responsibility of external structures that do not depend on the investigators (satellite centres, home care nurses, specific remote monitoring measures, etc.).

National research funding COVID

Public funding

According to the ''Flash'' audit carried out by the Court of Auditors and published in July 2021, the total amount of resources allocated to French public research on COVID-19 amounted to a little over €500 million, excluding European funds [13]. Although notable, this financial effort remains significantly lower than that provided by Germany (three times more) or the United Kingdom (twice as much). The Ministry of Higher Education, Research and Innovation (MESRI) and the MSS have nevertheless mobilised to finance calls for projects (AAP), either directly, or by reformatting certain AAPs such as the Hospital Clinical Research Programme (PHRC), for example, or through the intermediary of funding agencies, in particular the National Research Agency (ANR). As the Court of Auditors points out, funding has been too dispersed to meet the challenges of the crisis and, as previously mentioned, the lack of organisation has undoubtedly accentuated the dispersal, while the direct allocation of some funding has lacked transparency. This situation was also exacerbated by the lack of coordination

recognized by all. The organisational efforts expected with the creation of the ANRS-MIE were late in coming and initially without additional resources. Finally, the chronic under-funding of structures remains a definite handicap, even if in the case of the COVIREIVAC vaccine research platform [11], the Inserm-DGOS accredited clinical investigation centres were able to mobilise quickly and efficiently. In the particular case of this platform, which was able to rapidly mobilise numerous research structures and enrol more than 50,000 volunteers in a few weeks, the problem was not so much funding but the delay in setting up the trials.

Industrial and private financing

At the public-private interface, as part of the ''Structuring Research and Development Projects for Competitiveness'' action of the PIA3, of which BPI-France is the operator, a special COVID-19 Structuring Project Call (PSPC) was launched at the end of March 2020, in order to support companies and public partners proposing therapeutic solutions against COVID-19. This PAA proposed to finance clinical trials on French soil for a maximum amount of €50 M per project. As of June 1, 2021, BPI-France had identified a total of seven projects for a total of €84 million in funding. In addition, the ''support and transformation of the industry'' action, also implemented by BPI-France, included a call for expressions of interest (AMI) designed to identify and support innovative projects whose potential was based on the development of new manufacturing and production capacities for the drugs needed to treat patients with COVID-19. By July 2021, 18 projects had been selected for more than €165 million. As for the industrialists themselves, we can highlight the development of a few clinical trials and the participation of several industrialists in the financing of therapeutic trials, notably by making available expensive drugs such as remdesivir or tocilizumab for example. Some small Biothechs have also contributed to the financial and research effort, but these financial flows are more difficult to identify precisely.

Some local initiatives

Research organisations, universities, university hospitals and CLCCs have also obtained, in varying but often significant proportions, European or private funding or have used their own resources to finance numerous projects. The *Assistance Publique-Hôpitaux de Paris* (AP-HP) has set up a COVID-19 emergency fund which has been able to collect numerous donations, including from large non-healthcare industrial groups, all of which have facilitated the organisation of care and the implementation of research projects [14]. Another example is the initiative of the I-SITE Université Lille Nord-Europe which, in addition to creating a Task Force bringing together all the health research players on the Lille campus, has made available a €2 million budget to support numerous actions related to care and, above all, to research on COVID-19. Finally, at the operational level, particularly in public structures, one can only regret the complexity of the financial circuits, which results in delays in the availability of funds and the obligation for academic promoters to make large advances of funds or even to work at the expense of other research activities.

Recommendations

To anticipate future health crises, several recommendations can be made:

- strengthen public/private financing tools and agencies such as BPI-France;
- provide ANRS-MIE with real budgetary autonomy and strengthen its capacity to generate PAAs in crisis situations;
- rethink and optimize the flow of public funds dedicated to research, both in crisis situations and outside of any health crisis;
- improve the sustainable funding of public research, preclinical and clinical structures as well as non-profit structures;
- give the Health Innovation Agency the ability to improve and simplify the way research is funded.

Other national issues

Research dedicated human resources management in times of pandemic

The development of the pandemic and the containment had a major impact on the management of human resources usually dedicated to clinical research activities in hospitals. On the one hand, many clinical studies were interrupted, and the staff in charge of them could be deprived of their activities or even confined to their homes. On the other hand, a lot of research work on COVID was being carried out, requiring a large number of people to be deployed in order to carry out or monitor it. Thus, in many establishments, in line with their participation in certain national projects such as the national cohort (Cohorte French COVID) or the DisCoVeRy therapeutic trial, all the investigation staff and even the staff of the Clinical Research and Innovation Departments (DRCI) were redeployed in order to meet the various needs. A particular effort has been made to enter numerous data in real time, possible cross-monitoring between the various academic promoters and work on the development and authorisation requests for numerous research projects with the merging of projects into a single project in order to optimise the future collection of data and the feeding of numerous sub-projects. Finally, it is important to underline the national mobilization of clinical research structures labelled by Inserm and supported by the DGOS, the Clinical Investigation Centres, which has facilitated the deployment of several large national projects such as the national cohort or, as mentioned previously, the COVIREIVAC platform [11].

Communication in turmoil

We can only observe a massive communication around COVID-19, whether it be the daily accounting reports presented by the Health Department, the emergence of new communication methods in the form of highly personalized YouTube channels or the rise in the use of social networks as a vector for sharing information on the pandemic, sometimes for the better but often for the worse. In this context, which is difficult for non-specialists to understand, several initiatives have been implemented to provide well

thought-out information, which has been popularized where necessary. These include the Inserm Detox channel [15], the information platform developed by the pharmaceutical companies (LEEM) [16], and the PHARMACOVID website developed under the aegis of the French Society of Pharmacology and Therapeutics (SFPT) with the aim of providing expert answers to all the questions that may have arisen on the subject of drugs and COVID [17—19]. Nevertheless, it must be noted that these varied and relevant initiatives have probably not been sufficient to inform and above all reassure the population in light of the flood of false information disseminated on social networks.

Recommendations

As a result of the discussions, the group proposed the following recommendations:

- develop ''research dedicated'' emergency response roadmaps at local or even national level in order to facilitate the redeployment of research support staff, particularly, but not exclusively, in hospitals;
- support and perpetuate scientific and medical popularisation initiatives by favouring independent institutional channels rather than political, governmental or industrial channels. To this must be added training activities for professionals and the general public on the issues involved in research;
- work more globally on more relevant and effective communication plans by focusing on delivering concerted and scientifically based messages, by calling on crisis communication professionals or by developing partnerships with the major national media, if possible by working on this communication with representatives of users and civil society;
- set up evaluations of how communication actions are received and understood, so that they can be adapted.

International issues

Steering and financing

As was the case at the national level, the international level is not generally advantageous either, particularly in terms of redundancy of tests, as has already been pointed out [2]. Nevertheless, we can mention the major impact of the work carried out in Great Britain through the RECOVERY trial [20]. This platform trial has succeeded in aggregating a large part, if not all, of the therapeutic research effort in the United Kingdom, with the recruitment of several tens of thousands of patients, making it possible to show the effect on mortality of dexamethasone [10] or tocilizumab [20] and to invalidate the therapeutic effect of several drugs such as hydroxychloroquine, lopinavir-ritonavir, azithromycin, convalescent plasma, colchicine or aspirin [21—26]. If such a power required the availability of significant funding, it is undoubtedly also the particular structuring of the British health system, associated with the pragmatism of the study's CRF, which made this possible. More generally, it is regrettable that at the European level there is a lack of joint steering and funding, which is probably partly responsible for the relative failure of the European deployment of the DisCoVeRy study. In this respect, the setting up of a European platform within the framework of the EU Response programme should in part enable this challenge to be met.

The recurring problem of data sharing

As the health crisis cruelly underlines, clinical research on drugs in general and that specifically related to COVID, suffers from a deficit of data sharing with quite different visions on the subject on the part of the many stakeholders. Paradoxically, in academic structures, there is sometimes more reluctance to share than in certain private structures. However, the implementation of agreements specifying the terms and conditions of sharing and the possible exploitation of the resulting analyses should be able to be developed without too many difficulties. It should be remembered that most publishers of major medical and scientific journals now require access to data that have led to publication, although implementation is still subject to varying degrees of approval [27]. Another point is the under-use or possible difficulty in accessing large databases in France, whether they are the national databases of the SNDS or the Health Data Hub or all the health data warehouses developed by university hospitals and other hospital establishments. At the same time, private stakeholders such as TriNetX are positioning themselves on this medical data market in order, under the guise of a partnership agreement, to aggregate data from different establishments on a global scale in order to, if necessary, develop them scientifically [28].

Recommendations

Under these conditions, the recommendations retained on these international aspects of the COVID health crisis were:

- establish a European Task Force capable of responding to health crises;
- strengthen the ECRIN infrastructure to facilitate the deployment of European therapeutic trials initiated in the event of a pandemic;
- strengthen public/private collaboration in order to pool forces in terms of human and technical resources and the production of new molecules, to ensure the greatest possible access for patients to innovative therapies;
- define more clearly the obligations for sharing research data.

Conclusion

There is no doubt that the health crisis, like its effects on the general population, has had a major impact on clinical research activities, particularly therapeutic trials. The frantic race to find an effective treatment has highlighted the strengths and, above all, the weaknesses of a globalized research system. Apart from the anti-COVID vaccine research, which led to the marketing of several vaccines in record time [29], it must be said that therapeutic research has not been as successful. It is true that the discovery of a treatment for respiratory viruses remains a challenge, and hoping to find a universal treatment for a disease with such a complex evolutionary history is undoubtedly a very difficult challenge. Nevertheless, in France, as in many other

countries, the organizations in place have not always been up to the task and their adaptation, even partial, has not been without difficulty.

The various recommendations outlined above can probably be summarized in three points: (1) to have a centralized structure capable of coordinating both preclinical and clinical research efforts that is accepted by all research stakeholders; (2) to set up agile and transparent circuits for the rapid provision of funding; and (3) to improve international cooperation to limit the unnecessary redundancy of certain research. Beyond the one-off actions implemented as a matter of urgency, the most important thing is undoubtedly the need to build a solid long-term research system in which public and private players can interact effectively for the common good and which can be deployed both for studies conducted in hospitals and in ambulatory medicine.

Disclosure of interest

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