Outpatient healthcare and clinical trials in the care pathway: Organisational and regulatory aspects and tools

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Summary

Clinical research in outpatient healthcare, particularly in general practice, which is the first line of contact with the population, is now a public health issue. However, this type of research has specific characteristics that differentiate it from clinical research conducted in a hospital setting and requires an adaptation of its conditions of practice:

- In terms of organisation, the development of research in outpatient healthcare relies on the appropriation of its fundamentals by the investigators, which implies their presentation, upstream, from the initial cycle, and the participation of practitioners in training modules adapted to research in primary care, such as those already organised by several GIRCI (*Groupement Inter régional de la Recherche Clinique et de l'Innovation* [French Interregional Clusters for Clinical Research and Innovation]). To compensate for the fragmented nature of their location, on the model of the EMRCs (*équipes mobiles de recherche clinique* [mobile clinical research teams]) in oncology, mobile research teams should enable general medical practices to participate in clinical trials. This presupposes, on the one hand, the allocation of earmarked funding to ensure the sustainability of a base of dedicated personnel and, on the other hand, the impetus of a national dynamic through the setting up of a multi-organisation thematic institute for "research in primary care" associated, at the operational level, with a national scale investigation network supported by a platform of excellence

- The use of digital tools and innovations (telemedicine; data collection via connected tools; e-consent; electronic signature) which make it possible to digitise and relocate all or part of the research procedures for both the participant and the investigation teams.

- An adaptation of the legal framework in order to bring the place of research closer to the patient and not the other way round, which means moving the equipment and investigations closer to the patient.

- Taking into account the acceptability of the patient, thus limiting the disruption that may be caused by his or her participation in a research protocol and motivating the practitioner by valuing his or her contribution and providing all the guarantees of scientific relevance and independence of practice.

In view of the contextual analysis, positive feedback and the availability of organisational and digital support points facilitating the delocalisation and digitisation of the conduct of research activity

as close as possible to the patient and his or her doctor, the round table concluded that opportunities exist today which favour the development of clinical research in general practice.
It is important to seize this opportunity and make the most of it without delay.

KEYWORDS

Clinical research; General practice; Training; Motivation; Mobile teams; Digitalisation; Digitisation; Patient, Acceptability

Abbreviations

ANRS-MIE: National Agency for Research on AIDS and Viral Hepatitis - Emerging Infectious Diseases (*Agence nationale de recherches sur le sida et les hépatites virales - Maladies infectieuses émergentes*)

ANSSI: French National Information Systems Security Agency

ARS *Agence régionale de santé* (Regional Health Agency)

CIC: clinical investigation centre

CNGE: National College of Teaching General Practitioners

CNIL: French National Commission for Information Technology and Civil Liberties

CST: clinical study technicians

CUMG: university centres for general practice

DIU FIEC: Inter-University Diploma - Training of investigators in clinical trials of medicinal Products (*Diplôme Inter-Universitaire - Formation des investigateurs aux essais cliniques des médicaments*)

DMG: departments of general practice

DRI: research and innovation departments

EC: ethics committee

EMRCs: mobile clinical research teams (*équipes mobiles de recherche clinique*)

EPST: public scientific and technological establishments

GCP: good clinical practice

GDPR: General Data Protection Regulation

GIRCI: French Interregional Clusters for Clinical Research and Innovation (*Groupement Inter régional de la Recherche Clinique et de l'Innovation*)

ITMO: multi-organisation thematic institute

MERRI: teaching, research, reference and innovation missions (*missions d'enseignement, de recherche, de référence et d'innovation*)

MSPU: university multidisciplinary health centre

ONDAM: French National Health Insurance Expenditure Target

PLFSS: French Social Security Financing Bill

PRO: patient report outcome

PUI: single use pharmacy

ROSP: remuneration based on public health objectives

SIGAPS: French system for interrogation, management and analysis of scientific publications

The theme of the participation of outpatient healthcare, in particular general practitioners, the "front line" of healthcare coverage for the French population and of the healthcare pathway, has already been the subject of several studies, reflections and feedback from experience. The participants of the round table whose analysis and recommendations are presented here, aware that many other ambulatory healthcare professionals could benefit from the reflection, chose to focus their approach on the involvement of general practice in clinical research. The main challenge is to include the general population and not selected patients in clinical trials, a condition that will make it possible to

develop professional recommendations, care strategies and therapies adapted to the most prevalent patient type [1]. While general practice academics write theses and research on their chosen topics using appropriate methods such as qualitative research, few randomised clinical trials of medicinal products or medical devices are actually conducted in outpatient settings.

To set the scene, it can be noted that although clinical research in general practice has existed for a long time [2], it has come up against specific difficulties in France and differs from the situation in other neighbouring countries such as the United Kingdom, which has a structured national general practice network.

The obstacles most often cited as hindrances to clinical research in outpatient healthcare are linked to three factors: i) the fragmentation of medical demographics, which is characteristic of private practice and freedom of installation, ii) the lack of both practice and availability of these potential investigators, iii) the continuous growth in demand for care linked to increasingly complex technical methods of care, which leave little time to devote to research within the time frame of the general practice consultation. French general practitioners manage an average active population of 900 patients in their capacity as treating physicians. Consultation time is constrained and lasts on average 16.7 minutes per patient to respond to 2.6 different reasons or problems, since this is the specificity of primary care medicine [3].

In making their recommendations, the experts at the round table took into account a range of new factors that are creating a different context and changing the practice of outpatient healthcare. The health crisis that has been sweeping across the world for almost two years has shown the need to be able to test innovative treatments and vaccine candidates very quickly, as soon as a COVID infection is detected. The sentinel role of detection and the ability of front-line practitioners to investigate and participate in research protocols have become increasingly necessary. The universitarisation of general practice, the health centres that have emerged and spreading throughout the country, and the techniques linked to the digitalisation of practices allow and facilitate a more sustained participation of outpatient physicians. The subject is topical and at the heart of several recent reports, including that of Professor Patrick Rossignol “Clinical trials in an epidemic context” [4]. The improvement of recruitment in outpatient trials and the participation of primary care healthcare professionals in patient enrolment was also the subject of a referral to ANRS-MIE[1] by the Minister of Health in early June 2021.

[1] ANRS-MIE: new agency set up in 2021, the National Agency for Research on AIDS and Viral Hepatitis - Emerging Infectious Diseases [*l’Agence nationale de recherches sur le sida et les hépatites virales - Maladies infectieuses émergentes*]

This article is based on the reflections of four sub-groups set up as part of the round table, one on organisational issues, the second on the use of technological innovations and facilitating tools, the third on the legal framework governing the practice and its recent developments, and the last on the criteria for patient acceptability and practitioner motivation. These four themes are the cornerstones of the development of clinical research in general practice, which is now a public health issue.

Organising clinical research in outpatient healthcare, taking into account the specificities of the practice

In terms of the organisation of clinical research activity, the specificities of outpatient practice to be considered are diverse and often differ from those encountered in hospitals: specific research themes, the possibility of reaching and enrolling people who are rarely enrolled in research (disadvantaged, rural, etc.), a wide variety of practice settings (group practices, training supervisors, etc.), the lack of time dedicated to research, sometimes a lack of facilities and a lack of support for research by appropriate staff.

Raising awareness and training outpatient practitioners

The development of research in primary care depends on highlighting the value of participating in research during the training of practitioners, both during initial and in-service training. Indeed, producing sound scientific results is a cornerstone of evidence-based medicine. For that, a minimum level of knowledge of research methodology and good clinical practice (GCP) is required of investigators. Training in research is also part of the continuing medical education programme for general practitioners. There is training in GCP or research methodology, sometimes focused on primary care issues, offered by some GIRCIs[2]. The GIRCI Grand-Ouest thus offers specific training in primary care research. The GIRCI Île-de-France offers a free web platform for self-assessment of knowledge and mastery of GCP in clinical research, which can be carried out entirely remotely. These training tools and materials could be open to outpatient practitioners or at the national level (e.g., DIU FIEC [*Diplôme Inter-Universitaire - Formation des investigateurs aux essais cliniques des médicaments* (Inter-University Diploma - Training of Investigators in Clinical Trials of Medicinal Products]), for the training of clinical trial investigators, which is already open to any physician interested in research) and could possibly be supplemented by specific training within the framework of continuing professional development, the latter benefiting from a valuation to be defined in order to encourage general practitioners to participate.

Bringing research to the patient: mobile research teams and units

For outpatients to have access to research, it is necessary to propose local organisations that allow research staff to meet them where they are: at home, their place of work or vacation, in their school, in an elderly care facility, in a nursing home or even in a medical facility such as an outpatient physician's office, a health centre, a clinic, a hospital, etc.

Mobile investigation teams made up of nurses, clinical study technicians and study physicians make it possible to carry out the procedures required for research without having to move patients to healthcare facilities. In 2006, the French National Cancer Institute and the Ministry of Health set up

[2] GIRCI: French Interregional Clusters for Clinical Research and Innovation. They are in charge of developing and coordinating clinical research in their territories, guiding project leaders and supporting applied health research activities carried out by healthcare institutions or outpatient healthcare facilities.

mobile clinical research teams (EMRC) to support researchers in healthcare institutions with emerging cancer research activities and thus encourage their participation in clinical trials. The EMRCs support investigators in all clinical research activities, in private or public institutions [5], and are often shared between institutions. Although outpatient care procedures have long been carried out at home, certain procedures related to research, the management of research products, their reconstitution and/or administration and monitoring after administration, the management of biological samples, and the technical processing of samples prior to transfer to storage facilities, are particular points of attention.

A research bus has been used in Geneva since 1992 to carry out mainly epidemiological studies, such as the study described by Sandoval 2021 [6]. These mobile research units can have a variety of equipment and functions and can help to overcome the limited space in many general practitioner surgeries, provide time for the general practitioner with a mobile team staffed by a physician who can inform patients, collect their consents, randomise and enter data into the *e*-CRF. A mobile clinical investigation unit has just been set up at the Clinical Investigation Centre (CIC) of the Rennes University Hospital in the form of a vehicle equipped to carry out all or part of the various tasks described above. The economic model for this type of organisation needs to be clarified, including an analysis of travel costs and the financing of the purchase and maintenance of the vehicle and the equipment it carries. For example, the Rennes vehicle and its equipment were co-financed by the ARS (*Agence régionale de santé* [Regional Health Agency]), the Brittany region and Rennes metropole, while the operating costs should be borne by the university hospital and the research protocols. The legal status of this type of location is discussed further in the section on "regulations".

Setting up specific circuits supported by national and local organisations

The structuring of research in outpatient healthcare can be based on existing organisations such as learned societies, research bodies (INSERM), the national college of teaching general practitioners (*collège national des généralistes enseignants,* CNGE), departments of general practice (*départements de médecine générale,* DMG), clinical investigation centres (CIC) and the research and innovation departments (*Directions de la recherche et de l'innovation,* DRI) of university hospitals. Similarly, the University Centres for general practice (*Centres Universitaires de Médecine Générale,* CUMG), university health centres, and the presence of general practice interns in the

practices of training supervisors should encourage the emergence and conduct of clinical trials in general practice.

However, these structures lack expertise in design, regulatory submissions and the conduct of clinical trials in outpatient settings. The working group identified several areas for improvement:

- An increase in the number of academics in general practice, funding for research years, PhD scholarships.
- Support for local or regional networks of investigators, such as university lecturers in general practice, by providing project leader time to design and conduct clinical research projects.
- The involvement and support of expert structures such as Clinical Investigation Centres (CIC), Clinical Research Units and Centres (URC, CRC [*unités et centres de recherche clinique*]), and hospital Research and Innovation Departments (DRI), which must be able to provide assistance and competent and available contacts to support the setting up and running of projects in outpatient healthcare: assistance with project design, methodological support, assistance with setting up and responding to calls for projects, and regulatory monitoring adapted to research in primary care. They may also be involved in the management of staff recruited for research in primary care: project managers, clinical research associates (CRAs) or clinical study technicians (CSTs), clinical study physicians. The initiative set up at the Nantes University Hospital is an interesting experiment with the creation of a Federal Primary Care Research Centre in the form of a consortium that brings together the stakeholders and structures involved in primary care (health UFRs, training schools, representative of the primary care teams / *maison de santé pluridisciplinaire universitaire* [university multidisciplinary health centre] (MSPU) of the research network, university hospital, health insurance, the Regional Health Agency (ARS), the Regional Council, and the various stakeholders participating in the research work and the professionals involved (URPS, CPTS, federation of health centres, professional associations, etc.).
- Specific calls for research projects in outpatient healthcare should be encouraged, as should the participation of general practitioners in clinical research projects in healthcare institutions.

There is also the national level where a federal organisation capable of developing, facilitating and coordinating the activity of these federal primary care centres needs to be put in place. Such an organisation could have two complementary components, scientific and operational:

- Creation of a multi-organisation thematic institute (*Institut thématique multi-organisme*, ITMO) for “primary care research” with a role of coordination and national scientific

leadership, based on the model of the Aviesan ITMOs housed in public scientific and technological establishments (*Établissement public à caractère scientifique et technologique*, EPST), following the example of what is done abroad for primary care research (e.g. Oxford, Cambridge, Harvard, UCL).

- Complemented by the labelling and support by a platform of excellence (such as Infrastructure F-CRIN) of a national scale network that brings together expertise and outpatient clinical investigation capacities with the corresponding funding.

Providing dedicated funding

Regardless of the system chosen, its roll-out is dependent on the allocation of earmarked funding to ensure the sustainability of a base of dedicated staff (project managers, coordination of investigator networks, etc.). This funding could come from a dedicated MERRI envelope integrating the SIGAPS (*système d'interrogation, de gestion et d'analyse des publications scientifiques* [French System for Interrogation, Management and Analysis of Scientific Publications]) valuation of publications resulting from research in general practice. The National Health Insurance Fund could participate in this funding via the ambulatory ONDAM (*Objectif national de dépenses d'Assurance maladie* [French National Health Insurance Expenditure Target]). The ARS could also finance a project leader or primary care research coordinator at the level of a structure or federation to boost research and provide support to investigators. Finally, research activity could be included in the ROSP (*rémunération sur objectifs de santé publique* [remuneration based on public health objectives] for physicians treating adults, which is annual and open to all self-employed and contracted physicians) to recognise and value the practice of research in the practice.

Specific calls for tender such as "RESPIR", a call for tender launched by the DGOS in 2021 and examined by the GIRCIs, should be continued and improved, both in terms of the timetable and the choice of themes, and in terms of the composition of the panels, so as to best represent ambulatory research. In particular, they would provide funding for human resources per research project.

Impact and conditions of use of digital tools and technological innovations

Today, many tools and services, particularly digital ones, are available to sponsors and investigators, making it possible to ensure the digitisation of all or part of the research process for both the participant and the investigation teams.

The health crisis was an undeniable catalyst in a system that was already receptive to the implementation of concepts and tools, some of which had existed for a long time but had not yet been integrated into the research framework and practice.

These tools include teleconsultations, information for patients and the collection of their electronic consents, as well as follow-up on the medical-administrative databases, as in the case of the Boulware study [7], which was carried out entirely in this way, with delivery of the treatments allocated by randomisation to the patients' homes.

One can imagine a multitude of regimens adapted to the patient, to the type of study and to the pathology. It can be envisaged that patients are initially seen and enrolled in outpatient facilities and that some of the assessment/technical examinations are carried out in hospitals, or that patients are enrolled in hospitals and that all or part of the follow-up is carried out in outpatient facilities. This return of the patient to his or her home and daily life facilitates acceptance of participation in the protocol and the collection of real-life data.

This appropriation of the new tools depends on a number of factors to be taken into account:

- Giving priority to the implementation in research of tools and services that have already been validated, authorised and used in routine practice and not to include a tool or service validation objective in the same research.
- Describing in a transparent and detailed way the tools and services proposed in the submission file to the competent authorities, focusing in particular on their interest, the process of use and safety.
- Ensuring data protection, taking into account the level of participation of trial subjects

To date, the decision regarding the terms of the contract with the sponsor or its representative, which could be made, for the sake of simplicity and speed, by "practice" or group of general practitioners, depends on the tool and/or the service subcontracted and on the sponsor's interpretation of the ICH-GCP guidelines (R2) - 4.5 and 4.6.

The reflection focused on four types of digital technologies for digitising research:

Telemedicine/Teleconsultation

The French Public Health Code defines Telemedicine as "medical procedures performed remotely by means of devices using information and communication technologies". Teleconsultation is one of the five telemedicine procedures defined by the HAS in 2019: "Teleconsultation allows a healthcare professional "to consult a patient remotely".

In the context of research, telemedicine/teleconsultation can be used to carry out a visit, or to monitor the administration of a research product to ensure patient safety, combined if necessary, with the presence of a nurse to administer the product and/or take vital signs.

The use of electronic follow-up visits in research should be clearly described in the protocol and the patient information leaflet. This point should be discussed with the patient during the briefing and consent should be given explicitly for this. In order to simplify their implementation, it is advisable to use telemedicine/teleconsultation as part of routine care. If this is not the case, the instrument will have to be validated in terms of data safety, compatibility with the various terminals, feasibility for patients and research sites and compliance with the GDPR, after having assessed the appropriateness of this method in terms of risks to the health of the individual. It will also be necessary to consider the potential recruitment bias engendered by this use if it is made compulsory; the use of online appointment booking tools could be a good indicator of this.

National and international bodies are questioning the validity in terms of "good clinical practice" (GCP) of the data collected by this means and whether or not it is necessary to record these remote consultations. The patient's home is a place of care. The question is whether it is also a place where research procedures can be carried out. The answer is yes, provided that the procedures performed are compatible with this place of practice in terms of safety for the individual. For the experimentation in patients' homes of a trial health product which does not have marketing authorisation or CE marking and which therefore does not constitute a validated and routine care procedure, the regulations should be specified.

E-information and *e*-consent

Remote patient information and his/her consent facilitates the presentation of research prior to initiating a consent process and allows continuous electronic access by the patient to updated information.

E-information and *e*-consent do not have the same implications and are not subject to the same constraints:

- *E*-information is not particularly problematic as it involves a different presentation of the information that allows the patient to decide whether or not to participate in the research. The "*e*" mode makes it possible to offer interactivity to the patient, who can consult information in variable geometry according to his or her needs and level of scientific knowledge. However, there is the question of the authentication of the person who will receive the information and the confidentiality of the mode of transmission of this information, which combines medical information and personal data. This information must be submitted to the ethics committee (EC) for approval.
- *E*-consent raises more complex issues and discussions are underway, led by the bodies on operational and regulatory aspects. One of the main points of discussion concerns the establishment of a means to ensure that the person solicited is the person who signs, with sufficiently reliable and robust evidence. *E*-consent is not rejected *a priori* but its implementation is subject to compliance with recommendations which are the subject of a working group in the European Commission as part of the Clinical Trial Expert Group. In France, a working group on information and consent procedures was set up in 2020 by the Ministry of Health. The development of IT solutions enabling secure electronic signatures is a factor that is conducive to the use of this method. It is recommended that this point be addressed in future versions of the reference methodologies published by the French National Commission for Information Technology and Civil Liberties (CNIL). It is probably not applicable to all types of studies and pathologies.

Data collection via connected tools

The use of connected tools including "patient report outcome" (PRO) for data collection at the patient's home or at the research site is not discussed here as it has already been detailed in a previous

session of the Giens pharmacology days [8]. It is recommended to use validated solutions and used in routine practice.

A question that subsists pertains to the ultimate recognition by the authorities of the data collected and their integration into clinical records.

Electronic signature

The electronic signature of the various research documents by all the stakeholders, which makes it possible to reduce collection times, is a major point that impacts and simplifies the setting up and conduct of research. The electronic signature is currently being rolled out and recognised by all stakeholders in France. The *Comité national de coordination de la recherche* (CNCR), representing the hospital-based valence of clinical research, has recommended to its members that the tool used for signing be referenced by the *Agence nationale de sécurité des systèmes d'information* [French National Information Systems Security Agency] (ANSSI) in accordance with the European *e*IDAS Regulation [9].

However, it is not possible to make a general recommendation on the level of security to be implemented with regard to the various documents, tools and services, since, on the one hand, different scenarios have to be considered (face-to-face/remote, in particular) and, on the other hand, the requirements of the stakeholders and, in particular, of the sponsors are not homogeneous, each being free to set the level of security that seems appropriate to them in light of their assessment of the risk. The *e*IDAS Regulation recommends the use of systems that allow a so-called "qualified" level of electronic signature to be reached, avoiding the reversal of the burden of proof of the authenticity of the signature. Compliance with 21 CFR Part 11 and GXP, standards defined in 1997 by the US FDA for the submission of documents in electronic format for research purposes, may be considered but is not a minimum requirement given the technical difficulty of use by investigators.

Other forms of digitalisation or use of new functions are contributing to the evolution of the traditional framework for designing and conducting a clinical trial. However, they were not explored in depth by the working group as they are not directly involved in the digitisation of procedures. These include:

- Recruitment via social networks and the internet are also among the tools and services that can help simplify participation and access to research.
- Training of investigation teams and the setting up of remote studies through e-learning and video-conferencing with recorded evidence.
- *E*-monitoring, although a critical topic, was considered outside the scope of the discussion as it does not directly impact on patient participation in research.

The legal framework for clinical research in general practice

As mentioned earlier, in ambulatory trials the research site should be closer to the patient, which in other words means moving the materials and investigations closer to the patient, rather than making the patient move unnecessarily. This assumption meets the requirements of Article L.1121-2 of the French Public Health Code (PHC) which states that "*No research involving the human person may be carried out: (...) if the research involving the human person has not been designed in such a way as to minimise pain, discomfort, fear and any other foreseeable inconvenience linked to the disease or to the research (...).*"

It should be noted that legal obstacles are often put forward as being able to block the conduct of clinical trials in outpatient settings, including the status of the research site and the investigator when they are outside a healthcare institution and the problem of dispensing the study treatments in the absence of a hospital pharmacy. However, an in-depth reading of the applicable texts suggests that, contrary to popular belief, it is legally possible to carry out ambulatory or virtual studies, although this relative openness of the legal framework must be accompanied by clarifications and certain adjustments to the regulations.

Therefore, it seems important to clearly state the legal basis for conducting such research.

Definition of "research location" and "site"

The research location is mentioned in Article L.1121-1 of the French Public Health Code (PHC) but not defined. See Article 1.33. of the Decision of 24 November 2006 laying down GCP rules for biomedical research involving medicinal products for human use: "*Location mentioned in Article*

L.1121-1 of the French Public Health Code, including a place of care, a hospital department or any other place where healthcare professionals practice, with human, material and technical resources adapted to the research and compatible with the safety requirements of the individuals involved, in which biomedical research takes place."

The location can thus be physically distributed over several locations/sites, with the patient being able to travel to medical/technical sites distant from the physical research location and directly dependent on the investigator for the purposes of the research. The research location is an entity working under the direction and supervision of the investigator, who is committed to the safety of the individual and the quality of data.

Article L.1121-13 of the French Public Health Code sets out the specific cases in which the location of the research must be authorised by the competent Regional Health Agency (ARS), thus determining the boundaries of the research location. In France, the notion of location has never been clearly explained with regard to the place of care, nor with regard to the delocalised management of patients ("satellite" centres) or even with regard to the location of the main research procedures in relation to the other procedures necessary for the research carried out whether or not under the conditions of current practice (which refers to the notion of "usual procedure" in Article L.1121-13 of the French Public Health Code). Clinical research could thus be understood as taking place in an extended geographical area and the notion of research location should be clarified and understood as the place where the healthcare professional carries out his or her consultation (including a teleconsultation) or the paramedical act, if applicable.

Similarly, the patient's home is a place of care that may become a research site or a component of the research site in which the investigator or healthcare professionals may work. As for any other research location, it must meet the requirements of paragraph 1 of Article L.1121-13 of the French Public Health Code which states that "*Research can only be carried out in a location with human, material and technical resources adapted to the research and compatible with the safety requirements of research participants.*" In the case of interventional research, the usual procedure, defined as a procedure other than that which the healthcare professional usually performs as part of his or her activity, must be understood as an adapted and secure procedure - even a new one - performed as part of the authorised research. It should be noted that Article 28 of the PLFSS (*Projet de loi de financement de la Sécurité sociale* [French Social Security Financing Bill]) [10] 2022 (currently under review by the Constitutional Council) wishes to introduce the notion of patients' domicile into the aforementioned Article L.1121-13.

The site is a methodological concept, not defined in the French Public Health Code, but specified in the E9 Guideline of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonisation process in Paragraph 3.2. entitled "Multicentre trials". This paragraph of the ICH E9 Guideline does not exclude the notion of a site with several clinicians recruiting in several locations, called "sub-investigators", but specifies that the notion of a site (of variable size and therefore corresponding to a notion of space rather than a single geographical location) must be defined for the trial under consideration and that measures to harmonise practices in the various components of the site must be implemented.

Definition and responsibility of the investigator

The investigator is defined by Article L.1121-1 of the French Public Health Code as "*The natural person(s) who directs and supervises the conduct of research on a location. If the research at a location is carried out by a team, the investigator is the leader of the team and is referred to as the principal investigator.*"

This article also specifies that "*when the sponsor of research involving the human person entrusts its implementation to several investigators in several locations in France, the sponsor shall designate a coordinator among the investigators*". The notions of "co-investigators" and equivalents of "sub-investigators" defined in the US regulations and in the ICH do not exist under French law, even though GCP designates "*the investigator's collaborator*" who may exercise, under the investigator's supervision, functions as part of the research or make important decisions concerning such research. This individual may or may not be a physician.

In the absence of a precise definition of research locations and of collaborators of the investigator who may practice on separate locations for research, with care procedures or certain procedures of research, it is difficult to legally qualify such locations and persons.

The notion of a "site coordinating" investigator had been envisaged for research carried out with outpatient investigators when the pharmaceutical law was amended to allow investigational medicinal products to be centralised with this "coordinator" for distribution to a group of investigators (see below).

It is desirable that the conduct of the same research in several components of a geographically extended research area, under the responsibility of a "principal investigator" relayed by the equivalent

of “sub-investigators” in the North American sense of the term, be made possible, provided that mechanisms are put in place to ensure that the “supervision and management of the research” can be carried out remotely based on the same quality standards. In this respect, Article 28 of the PLFSS 2022 (currently under review by the Constitutional Council) introduces the notion of “coordinating investigator per site or territory” in the case of research carried out by several investigators on several sites or territories in France.

The members of the round table call for a clarification of these notions of location, site and territory with a view to facilitating the implementation of research while preserving the safety of individuals and transparency on the identity of those involved.

These procedures for setting up research in several geographical components of a research location, comparable to a “single site”, would also make it possible to simplify and accelerate the contracting system, limit the number of open sites and maximise the number of patients enrolled in each component of the research location for a given clinical study.

Distribution of medicinal products

Prior to the choice of an investigational ambulatory drug delivery system, the level of knowledge of the safety profile of the medicinal product in the given indication should be assessed and clarified.

From a regulatory standpoint, there are three points to consider concerning the distribution system of the medicinal product in the context of research.

The draw and distribution to several identified data generating locations under the same site

Currently, it is possible to send treatments to patients from an in-house pharmacy (*pharmacie à usage intérieur* [single use pharmacy] PUI). For products requiring methods of administration other than per os, depending on the type of product, it is possible to consider self-administration or administration by a nurse. For safety reasons and as mentioned above, this administration can be combined with teleconsultation with the physician-investigator before, during and after the

administration. If the services of a nurse are used, it is conceivable that the nurse could transport the treatment from the pharmacy to the patient's home to administer it (as they do on a daily basis as part of their care); depending on the specific nature of the product, the treatment could be reconstituted in the pharmacy or at the patient's home or in the mobile investigation unit mentioned above.

Article R.5124-3-1 of the French Public Health Code states in paragraph 3 that "*When biomedical research takes place outside an institution mentioned in Article L.5126-1 which has an in-house pharmacy, investigational medicinal products may be provided by an investigator as defined in Article L.1121-1 to other investigators on an exceptional basis. This is mentioned in the aspects of the protocol provided for in Article R.1123-20 and is carried out in agreement with the sponsor and in compliance with Good Clinical Practice as provided for in Article L.1121-3 of the French Public Health Code.*" This article, created in Decree No. 2006-477 of 26 April 2006, was intended to facilitate research carried out by self-employed practitioners. This text, which makes the investigator a "pro-pharmacist" who centralises and distributes the products, is fully operational but is used only very rarely. It should be revised to include ancillary medicinal products.

Dispensing of investigational or ancillary medicinal products by retail pharmacies

The legislation only addresses this issue in the context of research using authorised products. Article D.5125-45-1, following Decree No. 2016-1537 of 16 November 2016 on research involving the human person, provides that *"Investigational or ancillary medicinal products authorised when used in the context of the provisions of 1° or 2° of III of Article L.1121-16-1 may be dispensed by retail pharmacies, if they are included on the list mentioned in the first paragraph of Article L.162-17 of the social security code (MA and conditions of reimbursement), and provided that: 1° the individuals participating in the research have the same characteristics as those covered by the authorised indication; 2° the research design does not require any particular manufacturing or packaging; 3° this research concerns medicinal products which, as part of the care, are dispensed in retail pharmacies; 4° the patients would have received these medicinal products if they had not been enrolled in these clinical trials; 5° the sponsor has put in place specific methods of monitoring compliance and traceability*"[3].

[3] This article has been suspended since 2019. Work on the draft texts is being finalised.

This article, codified in the French Public Health Code, allows the centralisation and dispensing of trial and ancillary medicinal products by retail pharmacies. However, the decree specifying the compliance and traceability rules has not been published. The members of the round table propose that the distribution criteria be broadened to include medicinal products being developed in this context.

The distribution of investigational medicinal products to patients

During the health crisis, the French authorities published guidelines allowing, in case of need, the delivery of investigational treatments to patients' homes, either from hospital in-house pharmacies or from dispensing facilities.

The requirements were:

1. No or minimal unnecessary movement of patients.
2. The transportation of the products in accordance with the temperature and environmental conditions defined by the sponsor in conjunction with the manufacturer.
3. compliance with the provisions of the General Data Protection Regulation (GDPR) and Law No. 78-17 of 6 January 1978 on information technology, data files and civil liberties, as amended, as well as the principles set out in the reference methodology (MR 001) adopted by the CNIL.

It should be noted that § 2.3.2 of MR 001, relating to subcontractors (transporters or distributors other than the sponsor), allows the delivery of products to patients under certain conditions.

Consideration of patient acceptance criteria and practitioner motivation

Research in primary care is being structured and developed in France under the impetus of the health authorities and general practice academics, gradually joined by other medical and paramedical stakeholders in primary care. Although research in outpatient healthcare can be conducted in a wide range of fields, in a variety of locations, with many healthcare professionals [11], it is illusory to try to develop it without questioning its feasibility from the standpoint of patients and practitioners [12].

Trying to duplicate clinical research in outpatient settings is nonsense and guaranteed to fail. The time frame of the general medical consultation determines this feasibility, both for the patient and for the physician. While hospital-based clinical research benefits from a long period of presence of the patient "within the walls" and from a multiplicity of professionals and interlocutors on site, at the patient's bedside, whether in full hospitalisation or on a day case basis, the "window" of recruitment and enrolment of consultants in general practice is very narrow. This is a twofold hurdle given that the physician has to take the opportunity of this very short time to present the research to the patient and convince him or her to participate. The motivation of the practitioner and the willingness of the patient to accept it is therefore a key factor in the feasibility of the research.

Patient acceptance

Patient acceptance depends on the timing of the research proposal to the patient, the practitioner proposing it, and the organisation of the study itself.

Proposing the trial at the right time

This is easy if the reason for consultation is related to the research project. However, if the patient meets the eligibility criteria for a study while consulting his or her general practitioner for a completely different reason, adherence to the project will be more difficult and may require the

secondary planning of a specific exchange, which requires the physician to take a proactive approach to screening his or her patient base and holding dedicated consultations. Eligible patients can be identified by a query on the medical record database, for example, or on databases referencing volunteers (the rarest case but the database of volunteers developed within the framework of CoviReivac, the national platform for testing COVID vaccine candidates, is an example) or through consultations with the general practitioner. Sometimes a search for eligibility on the physician's patient file may be necessary to initiate targeted requests. In this respect, harmonisation of the collection of computerised data from general practitioners should be encouraged, which would facilitate, through the compilation of such data, feasibility studies, recruitment in clinical trials and even [large]-scale cohort studies.

A known investigator promotes patient participation

Participation can be proposed by the general practitioner or the specialist who usually follows the patient. The fact that it is a practitioner whom the patient knows, favours the patient's confidence, and allows for a presentation and contextualisation of the study adapted to his or her particular situation. This may involve providing information about the study and then delegating enrolment but the initial contact from the usual carer is the key factor.

Research that is as close as possible to the usual care provided in outpatient healthcare

The organisation of the trial will weigh up its conduct *in situ* at the general practitioner's surgery versus in a dedicated site on the following criteria: logistics, constraints, costs, time, (un)usual contacts, follow-up rhythm close to habits, etc.

As provided for in applicable regulations, any distance from the patient's daily environment and usual means of seeking care is financially compensated for by means of compensation for the patient (transportation, loss of days worked, etc.). Factors that are not part of the usual consultation

rhythm can be digitised and sent by the patient on a regular basis: sending self-questionnaires, anthropometric data (weight, saturation, self-monitoring of BP, etc.), quality of life scales, etc.

Practitioners' motivations

The role of outpatient healthcare is to participate in all types of trials but its own role will depend on the complexity and adaptability of the study to outpatient practice.

The general practitioner must be convinced of the relevance of the research project and of the usefulness of his/her participation

Motivation can be twofold: the physician's personal interest in his or her area of specialisation. The tasks entrusted to them are flexible: patient recruitment, eligibility and inclusion, delivery of medication or filling case report forms. Commitment will be facilitated if the research improves the physician's professional practice by updating knowledge through appropriation of the protocol and after the study. It is important to work on the most common patient profiles, prevalent pathologies and transposable approaches for a large number of patients in the active patient list.

Reflecting on the academic or industrial dimension

Industrial promotion of trials can be a barrier to general practitioners' participation because of concerns about conflicts of interest with manufacturers. An academic primary care interface seems necessary to guarantee the scientific and clinical relevance of the study, its feasibility and the independence of the investigator.

Recommendations

Recommendations of the Round Table are detailed in the box below.

RECOMMENDATIONS FOR DEVELOPING CLINICAL RESEARCH IN GENERAL PRACTICE	
Raising awareness and training general practitioners	Promoting training: - initial training via compulsory modules in research methodology and good clinical practice (GCP) - continuing education via a training programme adapted by university departments and the GIRCIs
Enabling research to meet patients wherever they are	Deployment of mobile clinical investigation teams throughout the country
Setting up specific national and local organisations	**1.** Support from the Hospital Research & Innovation Departments for the design and conduct of trials **2.** Creation of a national federal structure (Multi-organism Thematic Institute (ITMO) for research in primary care/Aviesan) **3.** Pooling investigative expertise via labelling and support by the F-CRIN Infrastructure
Dedicating earmarked funding	**1.** Dedicated MERRI share integrating SIGAPS valorisation of publications resulting from research in general practice **2.** Continuation of targeted funding initiatives (calls for projects)
Promoting the digitisation of clinical trials through the use of digital tools	**1.** Telemedicine and teleconsultation **2.** E-information and e-consent **3.** Data collection via connected tools **4.** Electronic signature
Clarifications and precisions to be made to a legal framework which, on the whole, is not opposed to the exercise of clinical research in ambulatory care	**1.** Conducting the same research in several components of a geographically extended research area, under the responsibility of a "principal investigator" relayed by the equivalent of "sub-investigators", in the North American sense of the terms (provided that mechanisms are foreseen so that "supervision and management of the research" must be made possible remotely based on the same quality reference systems). The group calls for a clarification of these notions of location, site, territory and principal investigator with a view to facilitating the conduct of research while preserving the safety of individuals and the transparency of the identity of those involved. **2.** Texts to be completed for the distribution of medicinal products: - Addition of ancillary (and not only investigational) medicinal products to paragraph 3 of Article R.5124-3-1 of the French Public Health Code.

	- Publication of the decree that specifies the compliance and traceability rules for the centralisation and dispensing of trial and ancillary medicinal products by retail pharmacies. - Broadening the distribution criteria by including medicinal products being developed in the mechanism.
Promoting patient acceptance	**1.** Given the time frame of outpatient healthcare (limited medical consultation time), the feasibility should be assessed upstream and eligible patients pre-identified by setting up patient referral databases. Harmonisation of the collection of computerised data from general practitioners should be encouraged (e.g., via a partnership with the French National Health Insurance) **2.** Facilitate the conduct of the trial as close to the patient as possible by limiting constraints (digitisation and mobile teams)
Motivating general practitioners as potential investigators	**1.** Valuing the fact that their participation will improve individual and collective professional practice. Hence the importance of working on the most common patient profiles, prevalent pathologies and transposable approaches for a large number of patients in the active file. **2.** Encourage participation in industry-driven clinical research by establishing an academic primary care interface to ensure the scientific and clinical relevance of the study, its feasibility and the independence of the investigator.

Conclusion

After analysis, all the factors seem to be in place today to develop clinical research in outpatient healthcare, in general practitioners' offices. A window of opportunity is open:

1. Spurred on by the COVID-19 pandemic, public authorities have become aware of the importance, in terms of public health, of associating outpatient physicians with clinical research, given their position as the first point of contact with patients who are currently rarely approached by clinical trial sponsors because they are not easily accessible
2. The emergence of identified stakeholders, such as the CNGE
3. Digital media allowing the partial digitisation of clinical trials, thereby making it easier to conduct them in outpatient healthcare
4. A legal framework which, provided that a certain number of clarifications are made, does not prevent practices from being adapted to the mode of practice and organisation of general practice
5. Promising local experiments

To initiate the development of this new aspect of clinical research, four conditions must be met:

1. Raising awareness and qualifying outpatient practitioners through initial and ongoing training adapted to their practice
2. Dedicated funding allowing, in particular, the deployment of mobile investigation teams
3. Cooperation of all stakeholders at national and local level
4. Recognition of the scientific specificity of clinical research in outpatient healthcare

These four conditions constitute the roadmap of a strategy to achieve a goal, the development of clinical research in general practice, which, today, seems to be accessible.

Disclosure of interests

Authors have no competing interest to declare

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