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Review

Regulatory aspects of prospective and retrospective clinical research in France in 2018

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ABSTRACT

In France, the so-called "Jardé law" (named for its proposer) on human research, implemented since 2016, defines the regulatory and legal framework for "prospective" studies, formerly known as "biomedical research" or "common care". Three categories are distinguished: type 1 is at-risk drug or non-drug interventional research, type 2 is low-risk, low-burden interventional research, and type 3 is non-interventional research. The decrees of April 12, 2018 precisely define a list of research categories for types 2 and 3, thereby clarifying the regulatory procedures. The Sponsor registers the trial on the database of the National Drug Safety Agency (ANSM), or the European EudraCT database for drug studies, to obtain an identification number. Regulatory procedures are undertaken with the IRB and ANSM and then the Data Protection Commission (CNIL). Retrospective research on previously collected data (other than genetic) does not come under the Jardé law, and is governed by the 1978 data protection law, updated by the application decree of December 2016 and the law No. 2018-493 of June 20, 2018 on protection of personal data. This article presents a clarification of the key methodologic and regulatory steps.

1. Introduction

The regulatory framework for human research in France was until recently set by the 2004 Public Health law, which replaced the so-called "Huriet law" to enable transposition of the EU Directive 2001/20/CE on good clinical practice in human clinical drug trials [1]. The so-called "Jardé law" (named for its proposer) on human research has been implemented since November 18, 2016 [2–5]. It defines a single legal framework and regulatory basis for "prospective" studies, formerly known as "biomedical research" or "common care". Three categories are pragmatically distinguished according to risk and burden: at-risk interventional, low-risk low-burden interventional, and non-interventional. The law defines the role and organization of institutional review boards (IRBs) and the mission and functioning of the National Human Research Commission (CNRIPH). It revises the framework and regulations concerning subjects involved in human research and informed consent. Changes have been made to reinforce monitoring and vigilance. Finally, the procedures to be undertaken in data collection have been clarified. The Jardé law is intended to mesh with EU regulations on human clinical drug trials, in a single mandatory legal framework for all national and multinational drug research, henceforth to be authorized via a single European portal [6]. Penalties are laid down for failure to respect the regulations (see Appendix A). "Retrospective" studies using previously collected data and not involving human subjects are not covered by this law, but come under the data protection legislation.

The present article describes these procedures didactically as an aid for physicians involved in clinical research.

2. Human clinical trials

2.1. Definition of types of human clinical trials under the Jardé law

The Jardé law distinguishes 3 types of human research (Fig. 1). The Sponsor is responsible for undertaking the regulatory procedures for each type (Table 1). Importantly, the IRB can reclassify a project from one type to another [2–5].

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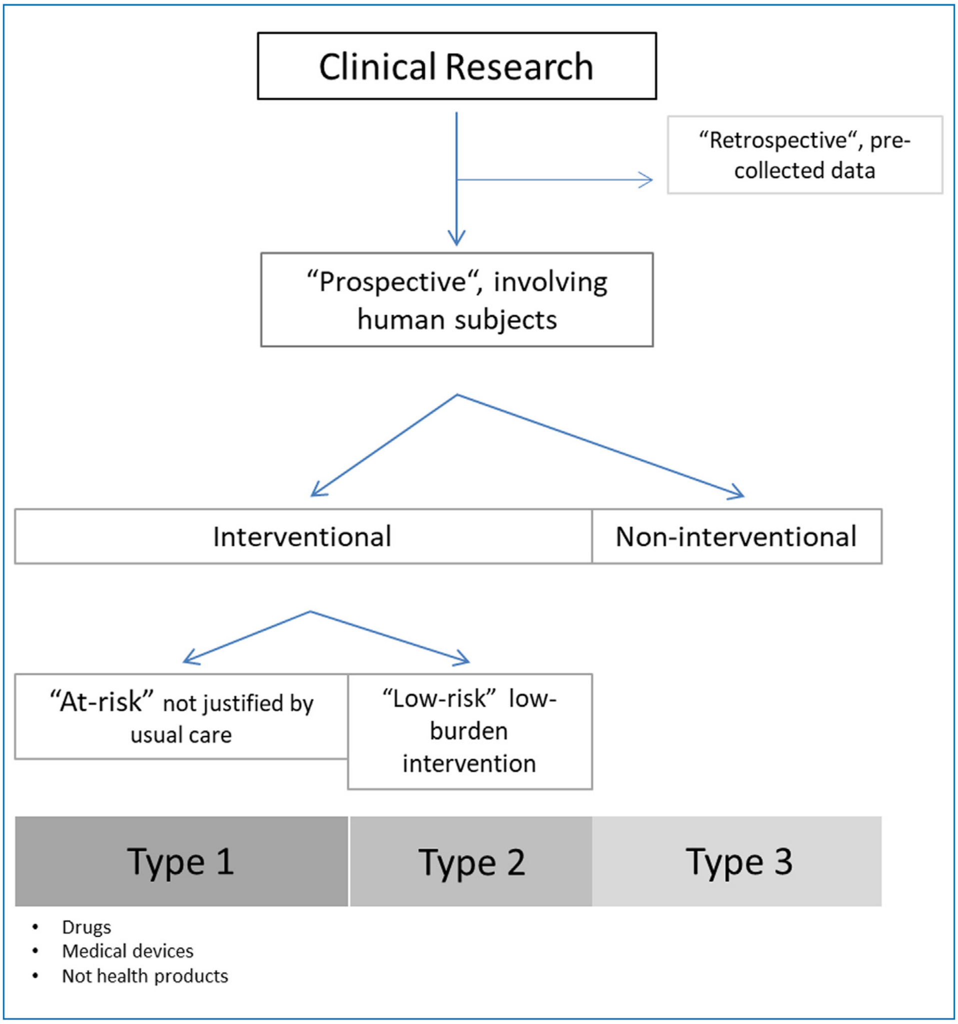

Fig. 1. Categories of human research according to characteristics.

2.1.1. *Type 1*

Type-1 human research is defined in Article L. 1121-1 of the Public Health Code as "interventional research involving intervention on the individual that is not justified by usual care" [2–5]. Such research involves intervention that is not free of risk. This comprises:

- drug research, for which the regulations should finally mesh with the EU regulations on human clinical drug trials [6];
- non-drug research on other health products (listed in Article L. 5311-1), including medical devices, products derived from the human body, and at-risk research not involving health products (e.g., studies of a surgical procedure, radiation therapy, and certain imaging examinations not counted as type 2 or 3).

2.1.2. *Type 2*

This is low-risk, low-burden interventional research as listed by a Health Ministry decree following advice from the General Director of the ANSM [2–5], dated April 12, 2018, and replacing that of May 3, 2017; it stipulates that the low degree of risk/burden is to be assessed with reference to the research participant's age, gender, physical condition and pathology (if any), and to the foreseeable risks associated with the type of intervention and its frequency, duration and possible combination with other interventions or products administered or used [7]. Appendix A of the decree lists 11 categories of authorized intervention:

- randomized attribution to diagnostic or medical strategies or interventions in common use;
- administration or use of products with market authorization under the corresponding conditions;
- administration of auxiliary drugs under conditions corresponding to their market authorization or safety and efficacy conditions borne out by convincing and proven scientific data;
- procedures usually performed as part of the research and not counting as type 3;
- venous blood samples with total volume calculated according to weight;
- biological samples other than blood (skin, tissue or extended biopsy, urine by probe, swabs of cervix, vagina, eye or nasopharynx, provoked sputum, amniotic fluid, cerebrospinal fluid);
- data collection and recording via sensors or imaging, not crossing the skin or mucosal barrier and respecting the manufacturer's recommendations or instructions for use, without injection of contrast medium or radiopharmaceutical;
- external mechanical, electrical or magnetic stimulation respecting CE labeling conditions or good practice guidelines;
- psychotherapy or cognitive-behavioral therapy techniques;
- certain other interventions concerning cosmetic products (stripping, hair sampling, ocular instillation, use test with superficial sampling, skin sensitivity test, minimal sun-screen test);
- interviews, observations and questionnaires the results of which are liable to affect usual medical treatment.

Table 1
Summary of characteristics of types of human research under the Jardé law.

Type of human research	Type 1 At-risk interventional		Type 2 Low-risk low-burden interventional	Type 3 Non-interventional
	Intervention not justified by usual care		List set by Health Ministry decree	List set by Health Ministry decree
	Drug research	Non-drug research		
Sponsor	Yes			
Insurance	Mandatory			No
Registration No.	EudraCT	ID-RCB		
IRB	Opinion			
ANSM	Authorization		Notification (study summary + IRB opinion)	
CNIL	MR001 conformity declaration or CNIL authorization			MR003 (or MR001 if consent required) conformity declaration, or CNIL authorization
Information and consent	Written information, written consent		Written information, express oral or written consent Pediatrics: a single parent may sign	Information and right of refusal (written consent: research coming under bioethics law)
National health insurance (*Sécurité sociale*)	Affiliation mandatory			Non-affiliates may participate

EudraCT: European Clinical Trials Database; ID-RCB: ANSM Clinical Biomedical Research ID No.; IRB: Institutional Review Board; ANSM: Agence nationale de sécurité du médicament et des produits de santé (Health Products Safety Agency); CNIL: Commission nationale informatique et libertés (Data Protection Commission); MR001, MR002, MR003: Research methodologies No. 001,002, 003.

2.1.3. *Type 3*

Type 3 is non-interventional research without risk or burden, all acts and products being applied in the usual manner, with a list drawn up by a Health Ministry decree on advice from the Director General of the ANSM [2–5,8,9]. The research may or may not concern health products, but studies, acts and products applied in the usual manner, with no supplementary or exceptional diagnostic, therapeutic or monitoring procedure. The most recent decree, of April 12, 2018, stipulates that absence of risk is to be assessed with reference notably to the research participant's age, gender, physical condition and pathology (if any), and to the foreseeable risks associated with the type of intervention and its frequency, duration and possible combination with other interventions or products administered or used [8]. Appendix A lists the 8 categories of such intervention:

- minimal supplementary collection of human body products during sampling for purposes of care, total volume being determined according to body weight;
- completely non-invasive collection of human body products (saliva, mucus, urine, stool, sperm, meconium, breast milk, colostrum, hair, nail, sweat);
- superficial swabbing of the skin, nose, auditory canal, oral cavity including oropharynx, anus and stoma;
- data collection by non-invasive sensors, respecting manufacturer's recommendations or instructions for use in the case of medical devices (electrocardiogram, electroencephalogram, electromyogram, magnetoencephalography);
- audio, video or photographic recordings, other than medical imaging;
- collection of electrophysiological data from material implanted or being implanted for purposes of care;
- non-invasive anthropometric measurements;
- interviews, observations, tests and questionnaires not jeopardizing the subject's safety or altering usual care, and with negligible burden or inconvenience for the subject.

2.2. *Sponsor and Investigator*

The Sponsor is the health authorities' main contact, and is defined by Article L. 1121-1 of the Public Health Code as the natural or legal person initiating and managing the research and ensuring that funding is provided for [2–5]. The Sponsor determines the objectives and means of data processing in line with Article 3 of the data protection law (*Informatique et Libertés*). The Sponsor must be domiciled within the EU.

The Investigator is necessarily a physician with appropriate experience in type-1 research. In types 2 and 3 not impacting medical management, the Investigator must be recognized by the IRB as duly qualified, without necessarily being a physician. The IRB ensures the appropriate qualifications of the Investigator, and the match between objectives and means. The Coordinating Investigator is the individual nominated by the Sponsor to direct and monitor the research when performed in several sites in France. The Principal Investigator is in charge of the team directing and monitoring the research when performed by a team in a single site.

Type-1 research cannot be launched without IRB approval and ANSM authorization. Types 2 and 3 cannot be launched without IRB approval and without informing the ANSM.

"Substantial" modifications are changes made post-approval, with significant impact on any aspect of the research, and notably on the protection of the individual, including safety, and on the conditions governing the validity of the research, product safety and quality, interpretation of scientific documents supporting the procedure or means of conducting the study. The ANSM and IRB, having taken position on the original project, give or withhold approval of such substantial modifications with respect to the initial application file [4]. The Investigator can make no changes to the study procedure with respect to the initial protocol or change the protocol without the Sponsor's agreement and without the change being set out in an amendment before being implemented [10].

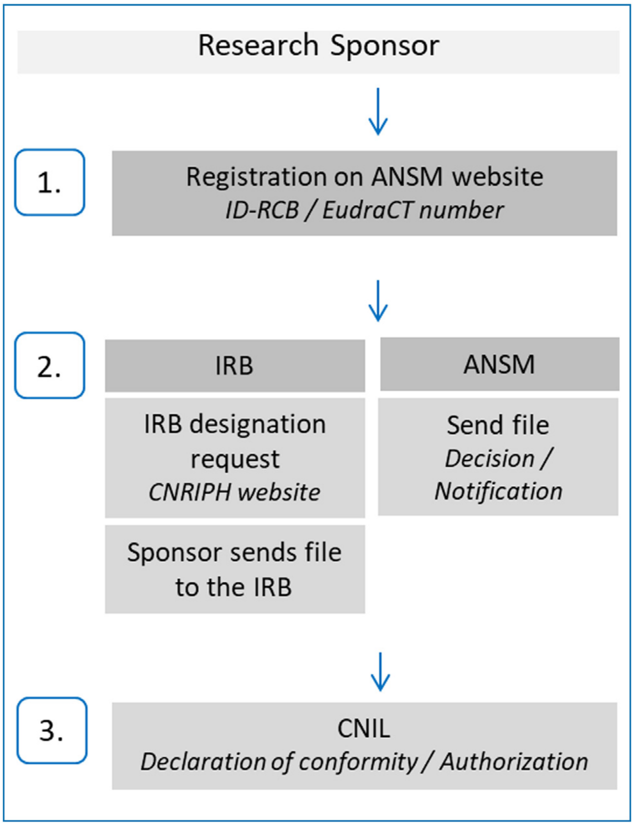

Fig. 2. Regulatory procedures for human research. IRB: institutional review board; ANSM: Agence nationale de sécurité du médicament et des produits de santé (Health Products Safety Agency); CNRIPH: Commission nationale des recherches impliquant la personne humaine (National Human Research Commission); CNIL: Commission nationale informatique et libertés (Data Protection Commission).

2.3. *ANSM and registration number*

The request for an ANSM biomedical clinical research ID number concerns all research except interventional human drug studies. The request is made by the Sponsor (Fig. 2) before application to the IRB on the ANSM website [11]. Instructions for use are available on-line [12]. The European Clinical Trials Database (EudraCT) registration number concerns interventional human drug studies, and is obtained by the Sponsor via the EudraCT database of the European Medicines Agency [13]. All research projects and results involving human subjects have also to be registered in an open-access database in line with the rules set out by decree: either at www.clinicaltrials.gov or in the EU Clinical Trials Register www.clinicaltrialsregister.eu.

Once the registration number has been obtained, the file is sent to the IRB for an opinion and to the ANSM for information or for authorization (depending on the type of research). Acknowledgment of receipt is sent to the Sponsor, with the authorized launch date id express authorization has not been given. Maximum application processing time is 60 days (which can be extended for innovative therapy drugs), whether the ANSM raises any questions or not. The ANSM takes position on individual safety, considering the importance of the research, the expected risk/benefit ratio, product safety and quality, conditions of use of products and subjects' protection with regard to the acts and methods employed and the scheduled means of follow-up.

2.4. *Institutional Review Board (IRB)*

In France there are 39 IRBs recognized by the Ministry of Health. The Board to which the project should apply is selected at random (Article L. 1123-6). This request is made on-line by the Sponsor submitting the project file on the National Human Research Conference (CNRIPH) website [14]. The file is then promptly sent by the Sponsor to the designated IRB. Acknowledgment of conformity is sent back within 10 days of reception of the complete application file, or else any missing documents are requested, with a fixed deadline. Approval status is delivered within 45 days. The procedure can be accelerated by a smaller committee for types 2 and 3. The Sponsor has 2 weeks to respond to any IRB demands, making the full processing time 60 days. In case of refusal, the Sponsor can apply to the Ministry for a second application to another IRB.

Applications may be made to the IRB and ANSM simultaneously or not, as the Sponsor wishes. The content list of the application is set by decree; lists according to type of research are available on the ANSM website [15]. The IRB judges the conditions of validity of the project, notably as regards data protection: appropriateness, exhaustiveness and intelligibility of written information provided, procedure for obtaining informed consent or non-refusal, and need for any period of reflection. The IRB's opinion also concerns the relevance of the research, risk/benefit ratio, match between objectives and means, investigators' qualifications, and the scientific and ethical value of projects to collect biological sample banks during the research.

ANSM authorization and IRB approval have 2 years' validity before launching the research. Prolongation can be requested, with a justification. The Sponsor should promptly inform the IRB and the ANSM of the new launch date in France, which is the date of the first informed consent signature by a participant in France (for types 1 and 2) or of the first non-refusal (for types 3).

2.5. *The CNIL and reference methodologies*

The Sponsor is responsible for data processing in human research. The reference methodologies set out by the Data Protection Commission (Commission nationale informatique et libertés: CNIL) provide a framework for processing information including health data. Reference methodology No. 001 (MR001) concerns interventional research (intervention on a human subject not justified by usual care, and intervention with minimal risk and burden) [16]. Reference methodology No. 002 (MR002) concerns non-interventional studies of in-vitro diagnostic devices [17]. Reference methodology No. 003 (MR003) concerns other non-interventional studies [18]. Reference methodology No. 004 (MR004) concerns research not involving human subjects (studies and evaluations in the health field) [16]. Reference methodology No. 005 (MR005) concerns studies requiring access to the institution's medical information databank (PMSI) and/or emergency admissions reports (RPU) by health establishments and hospital federations [17]. Reference methodology No. 006 (MR006) concerns studies requiring access to the PMSI medical information databank by health sector businesses [18]. The reference methodologies most widely used in clinical research are thus MR001 and MR003 (Table 2).

If the study comes under one of these methodologies, the Sponsor keeps an updated list of the relevant research. If the study does not come under a reference methodology, the Sponsor must request research authorization from the CNIL after IRB approval [12].

The Scientific Officer is appointed by the data processing officer (Sponsor), to whom he/she reports, and ensures the protection and respect of the objectives of data and processing. The Scientific Officer may for example be the Coordinating Investigator, or a methodologist. It is important that data are to be rendered

Table 2
Summary of characteristics of reference methodologies MR001 and MR003 as defined by CNIL.

CNIL reference methodology	MR001	MR003
Participant information	Individual	Individual
Participant agreement	Written or express	Non-refusal
Research type	Interventional	Non-interventional
Behavioral studies	Yes	
Photographs	Yes (NB: no possible identification)	
Genetic characteristics	Yes (unless identification or re-identification)	No
Type of data	Coded ID, health status, age or birth date (month and year), family situation, images, educational level, occupational life, living situation, consumption, activities, etc.	
Data conservation time	Until marketing or 2 years after last publication of results or, if no publication, until signature of final report; then archiving for ≥ 25 years depending on type of research	
Data security	No data entry except via processing tool; tool (CRF or eCRF) must be secure; secure messenger service or dedicated platform	
Data transfer	Those concerned must be informed, in line with RGPD rules EU: yes, no extra formalities Non-EU: possible, but if country ensures protection in line with RGPD rules	

CNIL: Commission nationale informatique et libertés (Data Protection Commission); MR001, MR002, MR003: research methodologies No. 001,002, 003; CRF: Case Report Form; RGPD: General Data Protection Regulation (*règlement général sur la protection des données*); EU: European Union.

anonymous, identity being coded. Only the health professional running the research in a given center can link the ID code to the person's forename and surname. The presentation of the data processing results must never allow direct or indirect identification of the participant.

2.6. Information and consent

The information is provided by the Investigator (physician or other qualified person) in the form of a document given to the participant. The document notably specifies the objectives, methodology and duration of the research, its expected benefits and foreseeable burden and risk, and any alternative medical solutions. It explains any necessary care provided after the end of the study, and in case of premature termination or of exclusion. It also explains the need for processing personal information in line with Article 57 of law No. 78-17 of January 6, 1978 concerning IT, data files and liberties. The regulations stipulate the requirement for individual information.

How consent is obtained depends on the type of research:

- type 1: free, informed written consent;
- type 2: free, informed, express (i.e., written or oral) consent. In case of particular methodological necessities incompatible with individual information, consent may exceptionally not be sought, information being collective; the IRB is competent to decide on this;
- type 3: right of refusal (with the exception that consent is required for research on genetic data).

If the subject is unable to provide consent in writing, oral consent is obtained if the person is physically present at inclusion. Otherwise, consent is obtained, or order of priority: from the designated "person of trust", a family member, or a friend on condition that this friend be wholly independent of the Sponsor and the Investigator. Information is given and consent obtained as soon as possible when the subject is able. In life-threatening emergency situations, the protocol submitted to the IRB may provide for inclusion without consent, information being provided and consent obtained secondarily.

If consent is withdrawn, data collected prior to withdrawal may be used unless the subject expressly refuses.

2.7. End of study

Two end-of-study steps are provided for in the regulations:

- end-of-study declaration. The date is defined in the protocol and usually corresponds to the last consultation with the last participant. The declaration is transmitted to the ANSM and IRB not later than 90 days after end of study (or 2 weeks in case of early termination for reasons of safety);
- final report, drawn up within 1 year of end of study (or 6 months for pediatric studies) and available to the ANSM on request. A summary is sent to the ANSM and IRB within 1 year of end of study (or 6 months for pediatric studies).

3. Research on retrospective data

Clinical studies on pre-collected data are analyses of personal data for the purposes of research, study and evaluation in the health field. They do not actively involve human subjects and therefore come not under the Jardé law but under the data protection law [19,20]. The procedures are mandatory. Authorization request files are to be signed by the representative of the data processing officer.

Procedures are centralized in a single secretariat of the National Health Data Institute (INDS) [21], which transmits them with 7 working days to the relevant committee. Table 3 presents the contents required in each file [20]. The file is transmitted for approval to the Health Research, Study and Evaluation Expertise Committee (CEREES). Approval is assumed by default 1 month after reception of the complete file. The CNIL may ask the INDS to determine the public interest of the research. After the decision by the CEREES, the INDS secretariat transmits the file to the CNIL for authorization. The INDS secretariat holds the information on the progress of the file until the decision of the CNIL is made, and makes it available to the person making the authorization request.

For research following MR004, no CEREES decision or CNIL authorization are needed (Article 54 of the data protection law, as modified by the very recent law on personal data protection, defining the mission of the CNIL in line with the General Data Protection Regulation (RGPD)) [19,20,22]. The data processing officers send the CNILM a single declaration of conformity with the provisions of MR004 for all intended data processing as long as this conforms to all of the provisions of the methodology. This declaration is made on-line [23]. The data processing officer keeps and updates a list of data processing operations under the methodology, and must register the data processing in the INDS's open-access registry [18].

Table 3
File contents for request for authorization of personal data processing for research, studies and evaluations in the health field, addressed to the INDS National health data Institute [20].

File contents for request for authorization of personal data processing for research, studies and evaluations in the health field
Name, address, titles, experience, functions and disclosure of interests related to the research for the data processing officer and officer in charge of the research, study or evaluation and, as appropriate, name and address of the sponsor and public entity making the request. When these are not domiciled in France or the EU, the name, address and function of their French representatives are provided The missions or object of the organization are also provided
The categories of those implementing the data processing and those with data access
Methodology of the study, evaluation or research protocol, specifying the objective of personal data processing, categories of those involved, origin, type and list of personal data and reason for use, duration and organizational modalities of the research, study or evaluation, data analysis method, and, as appropriate, rationale for sample size and method of observation or investigation
Type of publication of results by the party making the request
As appropriate, planned measures to communicate with those concerned by the data processing according to Article 57 of the law of January 6, 1978 or reason for request to be exonerated from this obligation. Requests concerning human research, studies or evaluations should include the project for the information document referred to in Article L. 1122-1 of the Public Health Code and express consent documents in line with Article 56
Data processing characteristics, and notably data conservation time
As appropriate, scientific and technical rationale for any request for exoneration to enable nominative data conservation beyond the time needed for the research
Previous decisions by scientific or ethical bodies
Planned collations or interconnections or other form of relation between data.
Provisions to ensure data processing security and legally protected secrets
As appropriate, any personal data transmission to a non-EU State
As appropriate, list of processing operations coming under VI of Article 54 of the law of January 6, 1978. In such cases, the file specifies the categories of data, the recipients or the categories of the recipients

4. Conclusion

The legal and regulatory framework for clinical research in France is based firstly on protection of the individual and his or her rights and liberty and data. The change from the Huriet law to the Jardé law now provides a single framework and basis for human research, extending the existing rules for biomedical research to all other kinds. This functional framework should in theory benefit both clinical researchers and research subjects.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Legal sanctions for non-respect of Jardé law

Conducting or organizing research referred to in paragraphs 1 or 2 of Article L. 1121-1 of the Public Health Code without obtaining free informed consent, in writing as appropriate, from the participant or those holding parental or legal authority or from other persons, authorities or organizations designated to provide consent for or to authorize research, as provided for in the Public Health Code, incurs 3 years' imprisonment and a fine of €45,000. The same penalties apply when interventional research is conducted despite consent having been withdrawn or non-interventional research is conducted despite the person's refusal.

Conducting or organizing research without IRB approval or ANSM authorization incurs 1 year's imprisonment and a fine of €15,000. Investigators conducting such research in breach of Article L. 1121-13 (research not in dedicated site) incur the same penalties.

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