# Results of the 2017 inspection campaign of French phase I/II research sites in Île-de-France following the BIA 10-2474 accident: Medical vs. regulatory relevance

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# THERAPIES

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# Results of the 2017 inspection campaign of French phase I/II research sites in Île-de-France following the BIA 10-2474 accident: medical vs. regulatory relevance

Inspection of phase I/II research sites

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**Summary**

*Aims.*- Following the serious adverse events that occurred in January 2016 during the BIA 10-2474 First-in-Human study, the French Ministry of Health asked the Regional Health Agencies to inspect operations at all research sites conducting phase I/II clinical trials of experimental drugs. The aim of this study was to assess the medical relevance of the inspections made in Île-de-France (Paris region) in 2017. *Methods.*- All 30 sites of Île-de-France region fully authorized to perform phase I/II trials were inspected by a public health physician and a public health pharmacist. Their reported list of observations was submitted to three physicians with longstanding experience of early pharmacology studies performed in academic or private research facilities. These physicians were asked to adjudicate each observation according to their perceived medical importance regarding safety. Adjudications were first performed separately and disagreements were later settled during a final adjudication meeting. *Results.*- At least one disagreement occurred initially among the 3 adjudicators for 84 of the 120 observations (70%) reported by the inspectors. Following reconciliation, the 3 physicians agreed that 20% of the observations were likely to have potentially serious medical consequences. These observations mainly concerned the management of emergencies and of serious adverse events and the continuity of care. *Conclusions.-* Maintenance of on-site inspections periodically carried out by regulatory authorities granting authorisations to perform phase I/II trials are justified. However, the medical relevance of these inspections can be improved with more emphasis on factors affecting the safety of research participants than on administrative or purely regulatory issues.

**KEYWORDS**

Clinical trials as topic; Quality assurance; Government regulation; Accreditation; Biomedical research

**Abbreviations**

ARC: authorized research centres

CIC: clinical investigation center

CRC: clinical research center

DGOS: General Directorate of Health Care

GCP: good clinical practices

INSERM: National Institute of Health and Medical Research

RHA: Regional Health Agency

## Introduction

According to French regulations, researches involving Humans which are not part of standard care, such as phase I/II studies, must be performed in authorized research centres (ARC). Authorizations are granted within each French region, by the Regional Health Agency (RHA) in charge of management of public policies defined by the Ministry of Health. RHA also oversees the operation of outpatients and of hospital and medico-social facilities. Authorizations of sites performing researches other than those of standard care are issued following an on-site inspection conducted by a public health physician inspector, and in the case of studies of experimental drugs or sterile medical devices, by a pharmacist inspector of public health. The inspection assesses the compliance of the research site organization with the regulations in force.

Following the tragic accident which occurred in January 2016 in Rennes (Brittany, France) during the First-in-Human study of BIA 10-2474, an instruction from the Ministry of Health asked the RHAs to inspect the operations of the research centres they had previously authorized to perform phase I/II trials [1, 2]. Thus, the 30 ARCs from the Île-de-France region (8 departments, 19% of the metropolitan population) underwent an operational RHA inspection as part of the ministerial instruction. In 2017, centres realizing phase I/II studies in Île-de-France represented about 51 % (30/59) of all French centres realizing such studies.

An analysis of all the remarks made by the RHA and of the responses provided by the ARCs was carried out in order to highlight the major points and possible areas for improvement. The purpose of this study was to assess the medical relevance of the observations made during these inspections in order to distinguish remarks concerning aspects considered medically important for the safety of

research participants from those concerning more administrative or regulatory aspects, considered less essential to guarantee the safety of research participants.

## Methods

### Implementation of inspections

The 30 ARCs authorized by RHA of Île-de-France to conduct phase I/II clinical trials were inspected between March and September 2017. Prior to onsite inspection, each ARC completed a questionnaire, designed for all inspections nationally and targeting good clinical practices (GCP), which was returned to the inspectors prior to their visit. During the inspection, the questionnaire was used as a basis for discussions between the RHA inspectors and the ARC team as well as other local health professionals (emergency care service, quality assurance department, hospital management, etc.). The onsite inspections were undertaken by a physician and a pharmacist, both public health inspectors.

Five physicians and 4 pharmacists inspected all sites in duet. All RHA inspectors had received the same training based on standard procedures for sites inspections. They assessed the organization and functioning of each ARC and its compliance with the regulations in force and with GCP. They focused the inspections on the prevention, detection and management of potential serious adverse events in volunteers. This included ensuring the transmission of information to the investigator and the sponsor.

All elements considered as malfunctions by inspectors were listed in an initial report together with observations of the inspectors. These observations were designated as “deviations” or “remarks” depending on whether or not they were linked to a legal reference, respectively. Warnings related to these observations were based on an estimation of risks to study participants. In the absence of risk or when risk was considered to be low, deviations led to “prescriptions” and remarks to “recommendations”. When the inspectors perceived a serious potential safety risk, be it deviations or remarks, “injunctions” were issued and a formal notice procedure was sent to the responsible physician of the ARC, requiring that corrective actions be promptly carried out. If these corrective actions were not judged adequate by RHA, sanctions were to be applied.

These prescriptions, recommendations or injunctions eventually resulted in an adversarial exchange between the RHA inspectors and the ARC responsible physician. Following the analysis of the ARC responses, a final report was written in order to assess the relevance of the proposed corrective actions and to make final recommendations, where judged appropriate.

**Assessment of inspections**

All inspections reports were summarized by one author (C.H.) in tabular form and submitted to the analysis of 3 physicians, independent of RHA, with longstanding experience of early clinical research in academic adult (C.F.-B.) and paediatric (F.D.) hospitals or in a private contract research organization (B.L.). The 3 physicians first separately assessed all observations, blindly from the type and location of inspected ARCs, by classifying them according to 3 levels reflecting their perception of potential medical importance (initial adjudication):

- Level 0: administrative criterion with no direct medical consequence on subjects' safety (no medical relevance).
- Level 1: far-reaching consequence on subjects' safety (minor medical relevance) (i.e. falling within the scope of procedures).
- Level 2: probable or possible consequence on subjects' safety (potentially serious medical consequences in case of failure).

Discordant adjudications among the experts were then discussed and solved collectively during a face-to-face meeting to obtain a unique adjudication of the potential medical consequences of each observation of the inspection reports (final adjudication).

A comparison of the distributions of the different adjudications was made between the dedicated and mixed ARCs, i.e. authorized research sites entirely dedicated to medical research and authorized research sites located in hospital departments performing standard care, respectively. Distribution were compared using Pearson's $Chi^2$ test. The total number of observations in dedicated and mixed ARCs was compared by use of Welch t-test. Statistical analyses were performed using R software (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria, 2017). Statistical significance was considered for p values $\leq 0.05$ ($\alpha = 5\%$).

## Results

One hundred and twenty observations were made after all inspections, including 5 injunctions, 67 prescriptions and 48 recommendations.

**Location and categories of inspected research sites**

Of 30 inspected ARCs, 18 (60%) were located in Paris, 9 (30%) in the department of Val-de-Marne, south-east of Paris, and 3 in other departments of Île-de-France. All ARCs were located in health facilities. No contract research organization had an ARC in 2017. Twenty five ARCs (83%) were located in public hospitals, mainly in University hospitals of Assistance Publique – Hôpitaux de Paris (N = 24) with one in Orsay hospital centre. Three other ARCs (10%) were located in cancer centres (Institut Curie and Institut Gustave Roussy), private institutions participating to the public service. The last two ARCs (7%) were linked to the Institute of Myology, a non-for-profit organization financed by patients and their relatives, the French Muscular Dystrophy Association.
Fourteen (47%) of these 30 ARCs were entirely dedicated to clinical researches, such as clinical investigation centres (CIC, accredited by the National Institute of Health and Medical Research [Inserm]) or clinical research centres (CRC, accredited by the General Directorate of Health Care [DGOS]). The 16 remaining sites (53%) were located in clinical services performing both specialized care and clinical research activities in hospitals.

Initial adjudications

The 3 physicians first performed their initial adjudications separately. Initial adjudications into the 3 categories of perceived medical importance are shown in Fig. 1.

Inter-observer agreement was poor. Eighty four of the 120 observations (70%) were not adjudicated with the same perceived medical importance category by all 3 physicians.

Disagreements were related to the following areas:

- Information of health staff: lack of a formal agreement with the various hospital services linked to clinical researches and lack of information from partner teams on current research protocols.
- Patient information: absence of information on the name of the service or protocol as well as on the action to be taken in case of serious adverse event on the card given to the patient.

- Management of emergencies: insufficient or absence of traceability and adequacy of the devices or drugs present in the emergency cart or of the training of research centre staff; absence of emergency simulations with the intensive care unit.
- Risk and quality management: absence of various procedures and designated referent.
- Drug handling.
- Compliance of the premises with fire safety requirements.

Table 1 shows the initial ratings of adjudicators according to the final adjudications.

Final adjudications

Final adjudications of the 3 physicians are shown in Fig. 2. Description of all observations and their classification is shown in table 2. Twenty-two observations (18.3%) were categorized by the experts as purely administrative, with no real impact on patient safety (level 0). These observations mainly concerned the absence of a formal contract with a pharmacologist, a legal requirement in France for ARCs studying new chemical entities, and deficiencies in the traceability of infectious wastes.

Seventy-four observations (61.7%) were judged to be of minor medical relevance (level 1). They mainly concerned the domain of procedures (drafting and updating of procedures), fire safety compliance of premises, issues related to drugs management and to the emergency cart (maintenance and traceability of medical equipment and treatments).

Twenty-four observations (20.0%) were judged to be of concern for subjects' safety and to be potentially associated with serious medical consequences (level 2). These observations mainly concerned the management of emergencies (training and information transmission), the management of serious adverse events (information on the patient's card, transmission of information to the investigator) and the continuity of care (insufficient on-call staffing).

Comparison of dedicated and mixed authorized research centres

The final adjudications of observations made in dedicated and mixed authorized research centres are shown in Fig. 3. There was a significantly higher number of total observations in mixed sites compared to dedicated sites (Table 3). However, there was no significant difference between the

two types of centres when considering the final perceived levels of medical importance (level 0: p = 0.39, level 1: p = 0.29, level 2: p = 0.51).

## Discussion

Monitoring of clinical research centres usually concentrates on purely regulatory aspects or performance metrics [3, 4]. While there are studies of the effectiveness of external inspections in improving standard healthcare [5], this is to our knowledge the first external analysis of a large and systematic campaign of regulatory inspections of clinical research centres performing early pharmacology studies aiming at assessing the medical relevance of these inspections. Inspections were motivated by the accident which occurred during the First-In-Human study of BIA 10-2474 in January 2016. This accident prompted the French Ministry of Health to reassess all authorizations granted to clinical research centres performing phase I/II studies in France. Many investigators [6, 7] but also some regulators are concerned by the medical relevance of the administrative burden, paperwork, and regulation associated with clinical trials. The importance of factors that guarantee the safety of research participants is emphasized by all, notwithstanding the need to guarantee the validity of the data.

The data reported here represent those of the Île-de-France region and may not reflect those of other regions. However, since in 2017 Île-de-France region hosted 51% of centres realizing phase I/II studies our results concern a sufficiently large set of centres to be informative of French practices. Although all centres were not inspected by the same duo of inspectors, all inspectors received the same training and inspections followed standard procedures which makes it unlikely that this constituted a bias in the reporting of malfunctions. The total number of observations was significantly higher in mixed than in dedicated sites but this was not the case when considering each perceived level of medical importance, possibly because the study lacked power to detect differences at each level. Also, a limitation of our study is that no data were available on centres characteristics such as duration and volume of activity, size of centres, staffing, type of drugs studied. Whether these features had an influence on the number and types of observations made by the inspectors was not studied.

Our study shows that the initial perception by investigators of the medical importance of observations made by regulators is highly variable (Fig.1 1, Table 1). Seventy percent of the observations made by inspectors were judged differently by the 3 adjudicators (91%, 72% and 46% for level 0, 1 and 2, respectively). However, there was less disagreement for observations classified

as medically important (level 2). It should nevertheless be recognized that there is a certain degree of subjectivity in the definition of the medical relevance of inspectors' observations. However, its is well recognized that adjudication committees limit the variable judgments made on clinical trial endpoints and that three members of such committees is sufficient for this purpose [8].

The perception of the potential medical impact of the observations was influenced by the practices and the experience of each adjudicator (types of research participants, adults or children studied; hospital or non-hospital structure). For example, the management of medical emergencies is different in an ARC located in a hospital and an ARC located outside a hospital where, among other aspects, the conformity of the emergency cart and the training for its use are perceived as more demanding than in the former because of the remoteness of an intensive care unit. It should be emphasized that several items classified as level 0 or 1 concerned formal traceability of procedures which does not necessarily mean that these procedures could not be implemented.

Adjudicators finally agreed on a classification of the medical importance of observations (Table 2) which allowed a final analysis of the 120 remarks made by the regulatory inspectors. Interestingly, the total number of observations was higher for mixed sites than for dedicated site. However, the perceived medical importance of observations made by regulatory inspectors did not significantly differ between ARCs dedicated to clinical research and ARCs located within clinical wards (Figure 3). This indicates that, within the scope of these inspections, procedures targeting the safety of research volunteers are not less demanding in hospital wards performing phase I/II studies than in sites entirely dedicated to clinical research studies.

Eighty percent of the observations were judged as unlikely to jeopardise the safety of research participants (level 0 and 1). However, 24 observations were judged as potentially associated with important medical consequences (level 2). These observations mainly targeted the management of emergencies and the quality of the chain of information transmission in the event of a serious adverse event. The adjudicators considered that these two elements are an absolute priority for the safety of clinical research participants and this was also considered to be the source of the consequences of the BIA 10-2474 accident [1, 7, 9]. Training of the staff involved in clinical trials, particularly for the management of emergencies and compliance with good clinical practices, raises the level of safety for research participants and is valued by sponsors [10].

Our study also highlights the difference between the administrative and medical nature of observations made by regulatory inspectors. Some injunctions, the highest administrative grade for an observation which represents a breach of regulation, are not necessarily categorized as having the highest potential for a medical impact (Fig. 2). Conversely 12 recommendations were

adjudicated as likely to have potentially serious medical consequences (Fig. 2). Regulatory constraints do not necessarily have a medical impact. For example, a formal contract with a clinical pharmacologist has not been shown to improve the safety of research participants. Depending on local organization it may be crucial to contract not only with an intensive care unit but also with an emergency service.

Importantly, the inspection campaign which was the subject of this study showed that, although all research centres were fully authorized to conduct early pharmacology studies, and, for several of them, had had a renewed authorization, malfunctions considered as medically important were found. This is even more significant since all the visited sites knew that the context of the inspections was directly related to the BIA 10-2474 accident, i.e. to safety issues and several of them follow quality assurance procedures [11, 12]. This demonstrates the importance of on-site visits by a regulatory authority before authorizing or renewing the authorization of research sites performing non-therapeutic pharmacology researches. However, our results, despite the limitations of the partial subjectivity of the adjudications, emphasize the need to differentiate the importance of administrative and medical objectives of regulatory inspections. We believe the medical aspects of clinical research should be the centre of regulatory inspections but also of audits [11] and inspections from sponsors. It should be recognized that administrative aspects should principally target those possibly impacting the safety of research participants and the validity of the data.

## Conclusions

The relevance of guidelines and regulations on the monitoring of clinical research and of research sites should be reconsidered bearing in mind the medical importance of monitored elements. On-site visits of monitors and inspectors remain essential to ensure the highest level of data quality and of safety for the volunteers participating to clinical researches.

## Disclosure of interest

Franck Odoul and Coffi Megnigbeto are employees of the Île-de-France Regional Health Agency. The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Île-de-France Regional Health Agency.
There are no other competing interests to declare.

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## References


[1] d'Autume C, Duhamel G. Enquête sur des incidents graves survenus dans le cadre de la réalisation d'un essai clinique (Tome 2) - Rapport définitif : observations et réponses des organismes et de la Mission. 2016. http://social-sante.gouv.fr/IMG/pdf/2016-012r_tome_2_rapport_definitif_enquete_incident_grave_essai_clinique.pdf. [Accessed 20 October 2019 (151 pp.)].

[2] Ministère des affaires sociales et de la santé. INSTRUCTION N° DGS/PP1/2016/208 du 27 juin 2016 relative à l'organisation d'inspections des lieux de recherches autorisés à conduire des recherches biomédicales. 2016. https://solidarites-sante.gouv.fr/fichiers/bo/2016/16-07/ste_20160007_0000_0082.pdf. [Accessed 20 October 2019 (2 pp.)].

[3] Macefield RC, Beswick AD, Blazeby JM, Lane JA. A systematic review of on-site monitoring methods for health-care randomised controlled trials. Clin Trials 2013;10:104-24.

[4] Walker KF, Turzanski J, Whitham D, Montgomery A, Duley L. Monitoring performance of sites within multicentre randomised trials: a systematic review of performance metrics. Trials 2018;19:562.

[5] Flodgren G, Pomey MP, Taber SA, Eccles MP. Effectiveness of external inspection of compliance with standards in improving healthcare organisation behaviour, healthcare professional behaviour or patient outcomes. Cochrane Database Syst Rev 2011:CD008992.

[6] Rule S, LeGouill S. Bureaucracy is strangling clinical research. BMJ 2019;364:l1097.

[7] Funck-Brentano C, Menard J. The BIAL/Biotrial case of death of a human volunteer in the first-in-human study of BIA 10-2474: Are we missing the fundamentals? Presse Med 2016;45: 719-22.

[8] Kahan BC, Feagan B, Jairath V. A comparison of approaches for adjudicating outcomes in clinical trials. Trials 2017;18:266.

[9] Funck-Brentano C, Ménard J. About fundamentals and sermonizers. Author's response to the letter on the article "The BIAL/Biotrial case of death of a human volunteer in the first-in-human study of BIA 10-2474: Are we missing the fundamentals?". Presse Med 2017 Mar;46(3):352-3.

[10] American Society of Clinical Oncology. Policy statement: oversight of clinical research. J Clin Oncol 2003;21:2377-86.

[11] Chevassus H, Duchesne C, Sailly A, Vigouroux C, Foulon C, Kubiak C, et al. Manuel de bonnes pratiques professionnelles des CIC - version n°2. Therapie 2017;72:525-38.

[12] Chesnais J, Fougerou-Leurent C, Laforest C, Renault A, Bellissant E, Laviolle B. Certification ISO 9001 d'un système de management qualité dans un centre d'investigation clinique. Therapie 2018;73:521-7.

**Table 1.** Initial ratings of adjudicators according to the final adjudications.

| Final adjudication | Initial rating: 1 adjudicator disagrees with final rating | Initial rating: 2 adjudicators disagree with final rating | Initial rating: All adjudicators disagree with final rating |
|---|---|---|---|
| **Level 0** | 4 | 15 | 1 |
| **Level 1** | 34 | 18 | 1 |
| **Level 2** | 9 | 1 | 1 |

Level 0: no medical relevance; Level 1: minor medical relevance; Level 2: potentially serious medical consequences.

**Table 2.** Classification of regulatory inspectors' observations by 3 physicians with longstanding experience of phase I/II clinical researches.

| | **Level 0**<br>**No medical relevance** | **Level 1**<br>**Minor medical relevance** | **Level 2**<br>**Potentially serious medical consequences** |
|---|---|---|---|
| **Contracts** | - No formal contract with a pharmacologist<br>- No formal contract with clinical wards (ICU excluded) | - No formal contract with an emergency ward or ICU | |
| **Training** | | - Lack of programmed alert simulations<br>- No traceability of team to basic life support training | - No training to basic life support: physicians, nurses, night team |
| **Information** | - No mention of the ARC name on patient card<br>- Lack of information to the responsible pharmacist in case of appearance of SAE<br>- No meeting records | - Lack of information of local wards on protocols dates and special provisions<br>- Absence of patient information on what to do in case of SAE (procedure) | - No mention of telephone numbers on patient card to allow contact 24/7 with the ARC or the investigator<br>- Failure to display emergency department or ICU phone numbers in the ARC |
| **Premises** | - Premises in poor condition | - Lack of timetable for fire safety compliance work<br>- Lack of accessibility to medical fluids<br>- Sanitary not suitable for overweight people<br>- Absence of secured archives and patient records | |
| **Materials** | - No fax in the ARC<br>- Deficiency of management of infectious wastes (no precise dates of constitution) | - Lack of traceability of emergency cart checks<br>- Emergency cart with non-disposable medical devices<br>- Absence of maintenance traceability and no maintenance plan<br>- Absence of risk management plan to maintain integrity of biological samples in case of power failure | - Missing emergency cart component (e.g. semi-automatic defibrillator)<br>- Inadequacy of emergency cart content to pediatric use for a centre performing pediatric studies |
| **Procedures** | - Lack of integration of the on-call procedure into the quality assurance plan | - Lack of or lack of updating of the SAE reporting procedure<br>- Lack of procedure to access the national database of research volunteers*<br>- Lack of procedures related to the | |

| | | | |
|---|---|---|---|
| | | monitoring of research volunteer, to the tracking of the experimental drug, or to the conditions for the transport of biological samples | |
| **Staff** | - No designated quality manager of the ARC | - No designated ARC responsible person for equipment maintenance<br>- Deficient organization allowing the rapid reporting of SAEs by authorized personal | - Insufficient nurse staffing requiring replacement of the RN by inexperienced nurse untrained to good clinical research practices |
| **Management of Drugs** | | - Substandard storage of thermosensitive products<br>- No indication of expiry date on oxygen cylinder<br>- Insufficient security to limit access to drugs held in the ARC<br>- Mismatch between actual and formal composition of the emergency cart | - Absence of certain drugs in the emergency cart |

24/7: 24 hours and 7 days; ARC: authorized research centre; ICU: intensive care unit; RN: research nurse; SAE: serious adverse event

* French law requires that research volunteers may need to be entered into a national database before inclusion to guarantee that an exclusion period following their participation to a preceding study is fulfilled and/or that the yearly limit of cumulated compensation of 4,500 € will not be reached if they are included.

**Table 3. Number of observations per research site.**

| | **All Observations** (n = 120) | | | **Observations adjudicated as likely to have potentially serious medical consequences** (n = 24) | | |
|---|---|---|---|---|---|---|
| **Observations per site** | Mixed sites (n = 16) | Dedicated sites (n = 14) | All sites (n = 30) | Mixed sites (n = 16) | Dedicated sites (n = 14) | All sites (n = 30) |
| Mean | 4.7* | 3.2 | 4.0 | 0.9 | 0.7 | 0.8 |
| Standard Deviation | 2.0 | 1.4 | 1.9 | 0.6 | 0.8 | 0.8 |
| Minimum | 2 | 2 | 2 | 0 | 0 | 0 |
| Maximum | 9 | 5 | 9 | 2 | 2 | 2 |

* $p < 0.02$ vs. dedicated sites

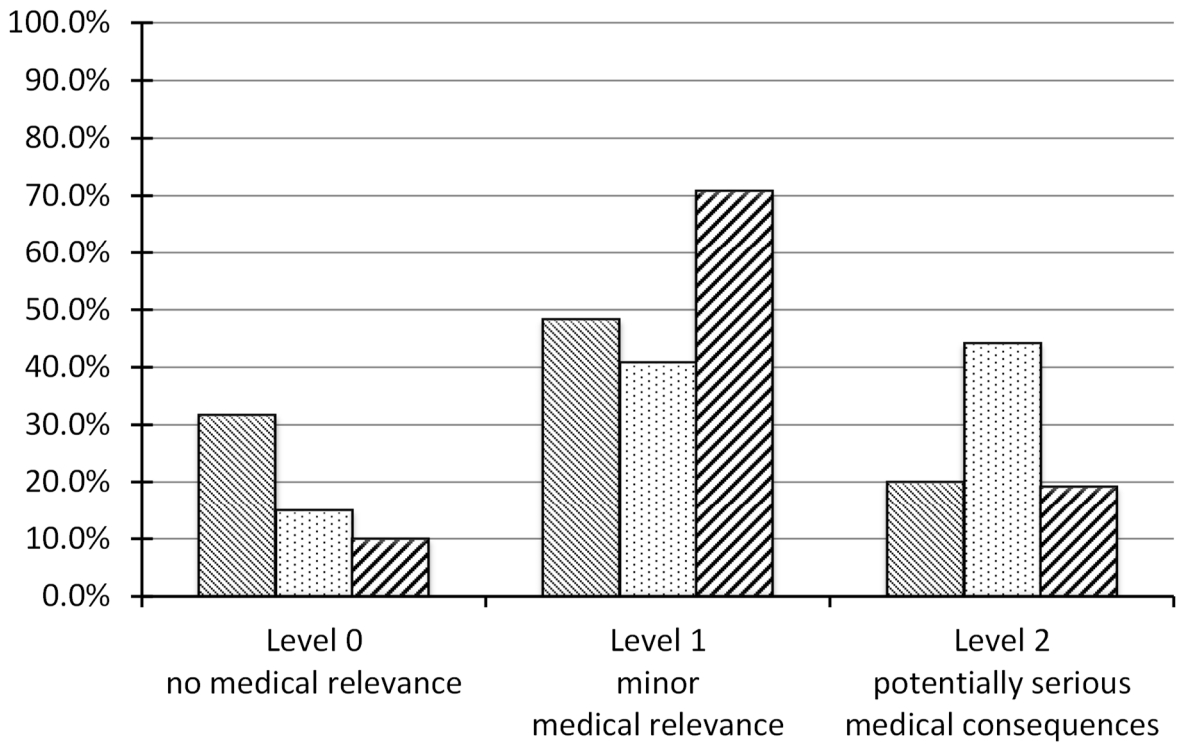


**Figure 1: Initial adjudications.** Initial adjudications of 120 observations made by the regulatory inspectors. Adjudications were made separately by 3 physicians. The percentages of initial adjudications made according to 3 levels of perceived medical risk (Level 0: no medical relevance; Level 1: minor medical relevance; Level 2: potentially serious medical consequences) are shown for each physician.

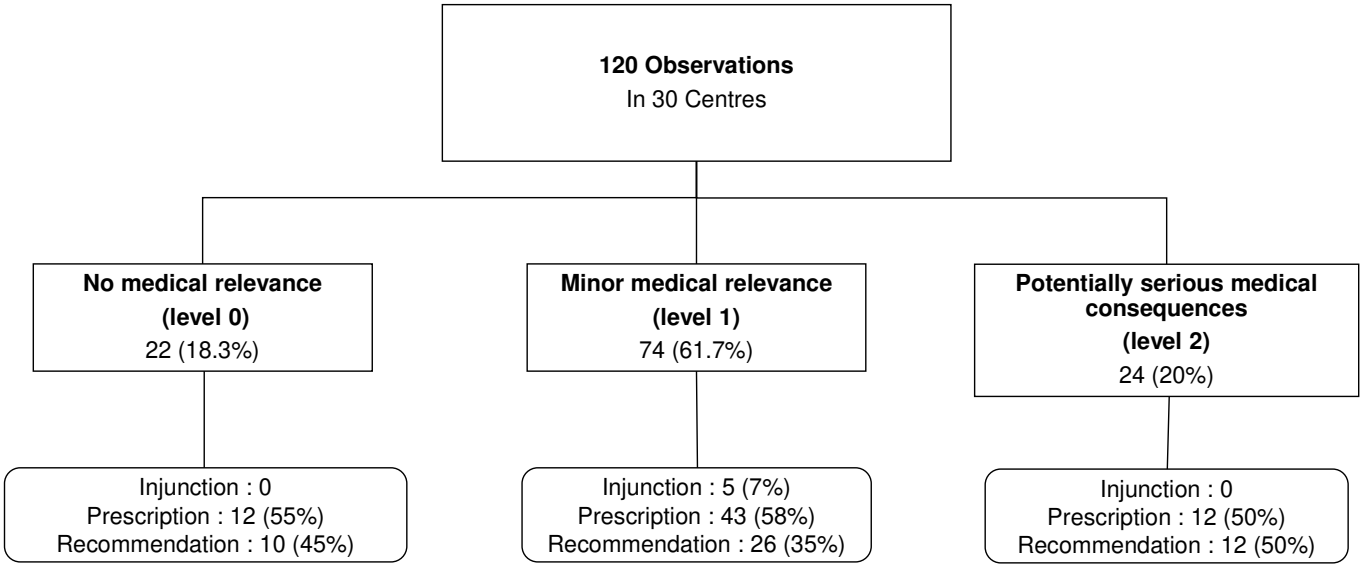


**Figure 2. Final adjudications.** The type of observation made by regulatory inspectors for each category of adjudication is shown at the bottom of the diagram.

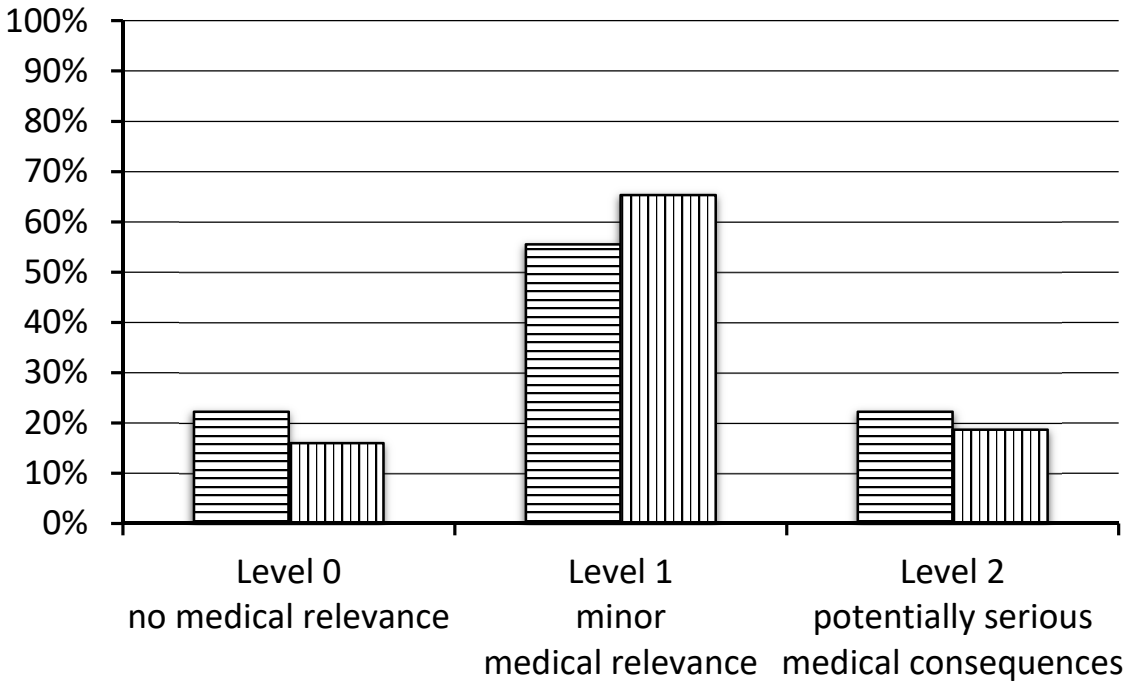


**Figure 3. Final adjudications of observations made in dedicated (left bars) and mixed (right bars) authorized research centers.** The percentages of final adjudications made according to 3 levels of perceived medical risk (Level 0: no medical relevance; Level 1: minor medical relevance; Level 2: potentially serious medical consequences) by 3 physicians are shown.