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CLINICAL TRIALS IN CANCEROLOGY: GUARANTEEING THE VALIDITY OF CONTROL ARM TREATMENTS

The unanimous opinion of plenary committee members present on 17th January 2022.

SUMMARY. — Although research on humans must respect numerous methodological, legal and ethical conditions, for various reasons the control arm treatment used in randomized control trials may not or may no longer be the gold standard. In such a situation, the clinical trial in question should not be initiated; if already underway, it should be interrupted. Yet this tenet is not always observed, which is a violation of the cardinal principals of medical ethics, i.e. the welfare and respect of individuals.

The committee raises the issue of insufficient secondary controls and interventions carried out by the relevant authorities authorizing a clinical trial due to practical and legal complications. In the event of control arm treatment obsolescence, as it currently stands, the trial sponsor – whether from academia or industry – assumes the role of both judge and jury in determining what action to take. The committee also raises the issue of a lack of interlocutors, both easy to reach and independent of the sponsor, who could register allegations of potential misconduct during a clinical trial.

The Ethics and Cancer Committee recommends that measures be taken to reinforce the continuous evaluation of the relevance of the control arm in randomized control treatment trials and that the standards be updated accordingly. It also recommends identifying or creating asingle point of contact, independent of the sponsors and investigators, where allegations of potential misconduct of clinical trials can be reported; the contact information should be given to all persons consenting to participate in research.

CASE REFERRAL — *Randomized control trials evaluate a treatment under study "experimental treatment") by comparing it to either a placebo or, as is usually the case in cancer research, to a standard treatment of the disease against which a new therapeutic is measured.*

An oncologist observes that trials undertaken in his department compare an experimental treatment against a standard treatment which was the gold standard when the protocol was designed; when the standard treatment becomes outdated, it is replaced by another more efficient treatment while the trial was underway. He reports that this situation is not explained to patients solicited to participate in these trials. Whatever the reason, He considers this situation a disadvantage for patients when compared to trials evaluating an experimental treatment against the best treatment available. He also finds it doubly noncompliant with ethics concerning medical practice and human research.

After trying in vain to alert the relevant institutions, he voiced his concerns to the president of the French Cancer League at the time, the late Axel Kahn, who in turn presented the case to the Committee of Ethics and Cancer, requesting the Committee's opinion on the ethics of these research practices.

OPINION: — Clinical research (that is, carried out on individuals at the bedside) is the motor behind therapeutic progress in all fields of medicine. Today, the methodological, legal and ethical aspects of research on humans must comply with international consensus as defined in numerous rules and regulations. In France, *drug* trials carried out on humans have been controlled by law since 1988, and a new law common to all countries in the European Union defining drug trials came into force in January 2022[1].

The expression "therapeutic" trial is often used to describe a clinical *drug* trial[2].

The protocol[3] of a trial involving humans must respect numerous methodological, legal and ethical conditions to guarantee:

1°) that it will allow a conclusion to be drawn (to provide an answer to the scientific question posed thus justifying the experiment) with a scientifically acceptable level of reliability.

2°) that the individuals involved have given their informed consent to participate in the study after having been given clear and straightforward information and that they will be completely protected against all futile acts or breach of trust.

The standard method of evaluating a new treatment is that of the *control* trial (the test treatment is compared to another treatment or to a placebo), that is *randomized* (the compared treatments are randomly allocated to the participants), and *double-blinded* (the allocated treatment is unknown to both doctor and patient)[4]. Clinical trials testing a new drug against another drug (the control), generally use the best available gold standard treatment as the control. Use of an old and outdated treatment to highlight the medical advantage of a new treatment is unjustifiable, both methodologically and ethically. The scientific knowledge gained would be of no interest. Also, patients participating in the trial would find themselves objectively placed in the disadvantageous situation of being exposed either to a treatment of

[1] In France: act n° 88-1138 dated 20 December 1988 (Huriet Act) supplemented (the most recently: act n° 2012-300 dated 5 March 2012 (Jardé Act); 2016 Ordinances, etc.), codified in articles L1121-1 et seq. of the French code of public health. —For all countries in the European Union: the European regulation EU 536/2014 of the 16th April 2014 relating to clinical trials of drugs for human use came into force on 31 January 2022.

[2] This expression is criticized because it leads to confusion on the nature of the treatment trials: their aim is indeed not to treat – although participation in such trials can have beneficial consequences for participants –, but rather to validate a hypothesis (in particular with regard to tolerance or efficacity). Even so, in certain situations in cancerology, the participation in trials can offer a better chance of a beneficial effect compared to standard treatments of low efficacy, or to the absence of treatement when none is available. For this reason, participation in a clinical trial can be proposed, in certain situations, as a relevant option.

[3] The protocol is the precise plan, detailed step by step, of the actions to be performed and the rules specific to the study that must be adhered to for its completion. The protocol notably includes a definition of the question which the study aims to address, the scientific justification of its interest, the determination of the number of participants necessary and the analytical method (statistical mainly) of observation.

[4] In cancer research, the double-blinded administration of treatment to both arms is rare, except for trials evaluating an adjuvant (a complementary product), for example a new antiemetic (drug to treat vomiting) against placebo or the gold-standard treatment (non-identifiable).

unknown efficacity – if the product is being tested, its efficacity is not recognized – –, or to a treatment which is known to be *inferior to the best treatment available*. The ethically acceptable situation to provide either a treatment of unknown efficacity or to the *best known treatment available.* Neither situation is without risk – the tested treatment may turn out to be less efficient than the standard treatment –, but at least disadvantages are kept to a minimum.

The referral to the committee imposes a discussion over the action that must be taken during a clinical trial in the event that the control arm drug is not or is no longer the gold-standard treatment. Such a situation requires discussion as it could be violating several fundamental ethical principles concerning research on humans and is likely to fail to comply with legal regulations as well – although the latter is outside the scope of the present opinion.

A complex reality

Various interviewed individuals involved in clinical research, in particular doctors and representatives of academic sponsors[5] or public institutions, state that the question of control arm obsolescence is regularly raised and believe that no authorization should be given for starting such trials and that trials in progress should be halted. These situations pose numerous difficulties with the end result being that, even if the cases are rare, certain trials that should never be authorized are launched and others that should be suspended are not.

Several potential reasons for this state of affairs include:

- *The long study period*. The design and implementation of a clinical trial is a marathon task, implying numerous specific skills and substantial resources. From an initial idea, the time taken to draw up a protocol, obtain financing and administrative authorizations, obtain involvement of investigation centers, for the recruitment and follow-up of patients, and the collecting and analysis of data can extend over several years.
- *The continuing evolution of scientific and medical knowledge.* Activity in clinical research is currently very high throughout the world, in particular in oncology. Last year, more than 84,500 clinical trials worldwide concerning cancer research were identified by a search on the website clinicaltrials.gov[6]. Between 2013 and 2018, the French national agency for the safety of medicines and health products *(Agence nationale de sécurité du médicament et des produits de santé*; ANSM) authorized

[5] The research sponsor is the institution, academic or industrial, taking the administrative and financial responsibility for the research. The doctor performing the research and in contact with the participants is the investigator; "the principal investigator" takes scientific responsibility for the research.

[6] Website consulted on the 23/09/2021 using "cancer" as the keyword in the search.

2,129 clinical trials concerning onco-hematology in France[7]. This intense activity has enabled therapeutic progress and an ever-increasing medical knowledge base. New discoveries accumulate and the recommendations for patient management evolve in accordance with the rhythm of advancement.

- *Sometimes long periods required for the recruitment stage.* Depending on the aims, the adopted methodology and the number of patients required, a minimum of a few months is needed for the recruitment of volunteers for a trial, however, this can often extend to years. In addition, this recruitment can be delayed by a number of different factors: competition from other trials concerning the same disease, poor organization, lack of engagement of certain research centers, etc.

Thus, the relatively long time taken to implement a clinical trial in a rapidly evolving context leads to an increased likelihood of the proposed control drug becoming obsolete during the development phase or once the trial has been initiated.

Yet the obsolescence of a control drug is not always easy to determine in practice, due to the inherent uncertainty of an evolving science. Indeed, any new research findings rarely meet immediate general consensus among the scientific community. Rather, early results presented at scientific conferences are often contradicted by later studies. All innovations require a phase of discussion and confirmation. In the field of oncology, therapeutic progress has mainly been incremental with few significant breakthroughs. The immediate interest of the related findings are thus more open to debate by the scientific community. Adopting new patient management strategies based on evidence from clinical research is a gradual process and takes time. One report or publication in favor of a better performing drug for use as the gold standard does not necessarily mean that a trial using the present gold standard in the control arm should be immediately accused of misconduct.

This also applies to treatments authorized in one indication and for which trials provide evidence of their promise in another indication. A therapeutic innovation of this type is not immediately accessible on prescription. Before that, numerous checks must be made, medico-administrative authorizations obtained and health insurance reimbursements activated, which in practice can take years. During this interval, any control drug for which a better performing alternative has been proposed and looks likely to take its place in the future, remains relevant and maintains the status of gold standard treatment.

[7] Lapière J, Christen C, Kerouani-Lafaye G et al. Evaluation of Clinical Trials in Onco-haematology: A New Method Based on Risk Analysis and Multidisciplinarity. Ther Innov Regul Sci. 2021 May;55(3):601-611. doi: 10.1007/s43441-020-00256-7. Epub 2021 Jan 27. PMID: 33502745.

Insufficient control of trials after authorization

Clearly, any randomized control trial with a control arm that is or has become obsolete should not be allowed to pass a second stage of checks by the French national agency for the safety of medicines and health products (ANSM), and be given approval by the French Human Rights and Ethics Committee (*Comité de protection des personnes*; CPP)[8]. ANSM adjudicates on the scientific relevance of the proposed research (minor questions or those that are already largely resolved do not justify a clinical trial) and on the safety of participating individuals. CPP considers the more ethical aspects, notably the conditions in which information is providd to the participants, how their consent is obtained, and the safeguarding of their human rights. However, in reality, due to practical and legal reasons, once a trial has received authorization, the level of control is considerably reduced. As such, the control arm of authorized trials for which the implementation takes 12, 18 or 24 months, may become obsolete and yet no mechanisms currently exist to stop the initiation of such trials, beyond the willingness of the investigators.

However, changing the control drug in a clinical trial constitutes a substantial change in the protocol, calling for new declarations and authorizations. Such a change in the middle of a trial is often inconceivable, from a purely methodological point of view. There is therefore a genuine temptation to not suspent a trial already underway or to initiate a trial in spite of the known obsolescence. The situation is far from being exceptional: one study estimated at 17% the portion of drugs having obtained marketing authorization in the US between 2013 and 2018 on the basis of randomized clinical trials involving a suboptimal control arm[9].

The current system controlling trials after authorization is in fact not designed or adapted to address these situations.

The ANSM can request complementary information from the sponsor at any moment during a trial. Should they suspect any risk to public health or that the conditions in which the trial is being undertaken no longer comply with those authorized, they can ask that changes be made to the modalities for implementing the trial, or decide to suspend or even ban the trial. However, such interventions post-authorization are rare and are only activated, in practice, in cases where attention has been drawn to the trial or, as with trials on the treatment of Covid-

[8] See articles 4, 7, 8 of the EU regulations n° 536/2014 (superseded on the 31 January 2022) to (very similar) provisions of the code of public health for other research.

[9] Hilal T, Sonbol MB, Prasad V. Analysis of Control Arm Quality in Randomized Clinical Trials Leading to Anticancer Drug Approval by the US Food and Drug Administration [published correction appears in JAMA Oncol. 2019 Jun 20]. JAMA Oncol. 2019;5(6):887-892. doi:10.1001/jamaoncol.2019.0167.

19, when public health imperatives impose them[10].

The CPP, on the other hand, cannot legally investigate any allegations of misconduct of an authorized trial. The Committee can only act following a request from the sponsor to examine any substantial modification made to the protocol; such an investigation is then carried out with the ANSM.

According to the interviewed cooperative groups,[11] all trials that they sponsor are regularly reviewed during meetings of their Boards of Directors Nonetheless, the relevance of the control arm is not systematically evaluated during these meetings.

Clinical drug trials are often – although this is neither systematic nor compulsory – monitored by an independent oversight board (*comité de surveillance indépendant*; CSI). Their mission is generally focused on analyzing reports of unexpected side effects, on verifying the constant maintenance of participant safety and on ensuring that the trial conditions permit the scientific credibility of the obtained results. The CSI of a trial notably has the power to call for an unblinding[12] in justified events, and even to recommend a suspension of the trial until a decision is reached by the health authorities. A recommendation document from the European Medicines Agency indicates that the CSI can take into consideration results obtained in other clinical trials, however it does specify that "such information from external sources should be evaluated with great caution and that any decision to stop or to modify a clinical trial based on such information should only be made in exceptional circumstances."[13] CSI oversight boards are insufficiently equipped to safeguard the scientific relevance of the control arm.

In fact, current recommendations describing what to do in the event of control arm obsolescence in a trial appear mostly to depend on the sponsor (whether from academia or industry), whose vested interests may cloud sound judgment.

Obstacles hindering allegations of misconduct

[10] According to interviewed representatives of ANSM, 140 clinical trials on Covid-19 were authorized during the first 18 months of the pandemic. When in summer 2020, corticoids became the gold standard treatment for the management of patients presenting severe forms of the disease, ANSM ordered all sponsors to ensure that changes were made to their protocol to integrate the new gold standard treatment and that all included patients received the corticoid treatment. Two trials were suspended as the sponsors refused to change the control treatment to the new gold standard corticoid.

[11] The cooperative groups are groups of academic sponsors active in a therapeutic field. The oncology cooperative groups (GCO) are a network of cooperative groups specialized in different cancers.

[12] The investigator is usually blinded to the treatment allocation between experimental or control drug, although this can be revealed to check whether any accident is caused by the experimental drug.

[13] Guideline on Data Monitoring Committee, Committee for Medicinal Products for Human Use (CHMP), EMA, July 2005. Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr.

Different systems and interlocutors exist where and with whom allegations can be made in the event of misconduct of a clinical trial. According to interviewed members of ANSM and the French National Cancer Institute (INCa), both organizations systematically address all allegations or queries raised concerning a clinical trial. In France, public and private organizations of over 50 employees including health care establishments where numerous trials are conducted, generally have systems in place to handle such allegations – and to protect whistle-blowers[14]. Information gathered that is considered susceptible to constituting a criminal offense can be addressed directly to the state prosecutor[15]… The media is another possibility, although it might be difficult to convey the significance of information concerning an obsolete control arm. In any event, experience suggests that for the public – and even for doctors – these systems are not well known of, are hard to access[16], or disproportionate.
The only point of contact for individuals concerned by the trials are the investigators and the sponsor, whose contact details are on the documents received at the time of consent; in other words, the parties at issue in the problematic situations described above.

Conclusions

1°) From an ethical point of view, situations in which trials continue with an obsolete control arm violate the cardinal principles of welfare and respect of individuals.
In research ethics, the French language uses the word *bienfaisance* as a translation of the English "beneficence". The notion conveys the dual idea of "doing something well" – technically or scientifically – and "doing someone good". The French *bienfaisance* carries a sense of charity that is not implied in the same way by the English "beneficence", which is defined as care to benefit others, and often expressed as "welfare". Welfare is the principal which establishes, in trial conception and conduct, the requirement for balance between expected benefits (for the individuals participating in the study and for the sick community) and risk linked to their participation. A clinical trial based on a question which is no longer of therapeutic interest, since the control drug is no longer relevant, upsets this balance and

[14] In France, these systems are defined by the law n°2016-1691 dated 9 December 2016 relating to transparency, the fight against corruption and the modernization of the economy, known as "Sapin 2".
[15] Article 40 of the code of criminal procedure obliges "all constituted authorities, public officers or civil servants who, while exercising their function acquire the knowledge of a crime or offense (…) to report it immediately to the public prosecutor along with any related information held".
[16] A certain knowledge of the clinical trial control system is required to even think of contacting the ANSM, for example. An appeal relating to a trial in onco-hematology made to the *Direction Médicale Médicaments 1* –DMM1 (drugs directorate) (who are committed to ensuring a response to any allegations) also requires deep knowledge of the system.

should not be conducted[17].

Such a trial also violates the principal of respect of an individual's independence and choice. Individuals participating in a trial are obviously not informed that they will not be given the best available treatment should they not be given the new experimental drug, but rather an outdated drug. They are consenting on the basis of incomplete or even misleading information. They are not in a position to make an informed decision to participate or not.

2°) On a practical level, the committee notes that individuals, be they patients or doctors, wishing to report misconduct of an authorized trial – obsolescence of the control arm being one -, currently have no easy-to-reach or identifiable interlocutor who is independent of the sponsor and investigator.

Proposed corrective measures

Several corrective measures have been envisaged during interviews with professionals and institutions when handling the referral.

1°) The first concern the modalities of controlling trials after authorization.

Introducing a « review clause ». Authorizations of randomized controlled trials of treatments could include a clause obliging the sponsor to provide a report at a certain interval (one year for example) after initiation of the trial and which would allow if necessary a re-assessment of the initial authorization. These reports would be addressed to ANSM and CPP. The introduction of such a review clause may pose a problem in terms of feasibility, the institutions concerned being already saturated by the flux in initial authorizations to deliver.

- *Updating the regulations.* The rules of good clinical practice (GCP) are regulatory decisions issued by health authorities (in this case the director of the agency responsible for the drugs). The GCP regulations in place for research date from 2006; they are quite specific with regards to "experimental drugs" (the drugs under trial), but there is almost no mention of control drugs and the control arm.
- Revising the missions given to the independent oversight board (*comités de surveillance indépendants (CSI)* in France). Missions entrusted to the independent oversight board monitoring, where applicable, a randomized control trial, are defined by mutual agreement with the sponsor of each trial. They could include ensuring the maintained relevance and credibility of the control arm, and the inclusion of this point in their recommendations.

[17] It should be noted that the running of such a trial does not conform with legal regulations either, thus making the sponsor susceptible to incur criminal liability.

2°) The second concern the modalities of making allegations of trial misconduct.

- *Creating a single point of reference for processing allegations of misconduct of authorized trials.* This unique gateway or ”office”, with a single telephone number and email address, will ensure the collection and processing of all allegations concerning the potential misconduct of authorized trials. Ultimately, ANSM, which already has a mission to ensure that order is maintained throughout the trial, would be the logical collection agent. However, we are again faced with a problem of means. An independent third party – typically an association – could doubtless effectively relieve some of the administrative load by participating in the front line management of calls to the single number and the filtering allegations.
- *Ensuring that the contact details of this office are provided to individuals participating in the trial separately from those of the sponsor and investigator.* The contact details of this office would be widely communicated and in particular on all documents given to participating individuals in a manner similar to the way that information on personal data protection is provided; the contact details of the French data protection agency (*la commission nationale de l'informatique et des libertés;* CNIL) being systematically indicated.

Recommendations

With these considerations in mind, the Ethics and Cancer Committee issues the following recommendations:

1°) that the ANSM and the French National Committee for Research Involving Human Subjects (*Commission nationale des recherches impliquant la personne humaine* ; CNRIPH) which coordinates the activity of the human rights and ethics committee (the CPP), enter into talks with the sponsors – from academia and industry – on the measures which should be taken to reinforce the continued evaluation of the relevance of the control arm in randomized control drug trials.

2°) that the regulations concerning good research practice be updated to include an imposed permanent relevance of drugs used in the control arm.

3°) that the contact details of a single data collection and processing office for allegations, independent of the sponsors and the investigators, be systematically provided on documents destined for individuals participating in trials. It suggests that associations participate in the operation of this office.

For citations: The Ethics and Cancer Committee, "Clinical trials in cancerology: guaranteeing the validity of control arm treatments", Opinion n°40, January 2022.

Key words: clinical trial, control arm treatment, experimental treatment, methodology, protocol, research, therapeutic progress, good practice, ANSM (*French national agency for the safety of medicines and health products*), CPP (*French human rights and ethics committee*), independent oversight committee, sponsor, investigator, whistle-blower, welfare, autonomy.

Interviewed persons:

- *Dr Nicolas Albin, oncologist and head of the Daniel Hollard cancer institute of Grenoble mutualist hospital group, scientific and medical advisor in onco-hematology on the ANSM advisory board for the assessment and monitoring of medicines in oncology and hematology.*
- *Dr Christophe Bardin, clinician and pharmacist, head of clinical pharmacy in cancerology and metabolic diseases at Cochin hospital, Paris. Member of the CPP Ile-de-France 1. Ex-member of the* French national committee for research involving human subjects *(Commission nationale des recherches impliquant la personne humaine, CNRIPH). Member of the vaccine strategy advisory board headed by Pr A. Fischer*
- *M. Pierre-Henri Bertoye, director of regulatory affairs, quality control and pharmaco-vigilance for Unicancer, president of the* French national committee for research involving human subjects *(CNRIPH)*
- *Pr Benjamin Besse, medical oncologist specializing in thoracic oncology, head of the Gustave Roussy medical oncology department.*
- *Mme Liora Brunel, head of the solid tumor research group of ANSM*
- *Mme Lucie Davenne, Clinical trial safety assessor for ANSM*
- *Dr Christine Donzel-Raynaud, thoracic oncologist in the respiratory medicine department of Argenteuil hospital (95)*
- *Pr Didier Dreyfuss, intensive care unit of Hôpital Louis Mourier (Colombes), member of the CNRIPH, head of the ethics work group for CNRIPH*
- *Mme Claire Dubois, project manager within the French oncology cooperative groups (GCO), a network of 10 cooperative groups.*
- *Mme Sonia Errard, Directorate general for health (DGS), biomedical research and practice quality control department (PP1*
- *Mme Laurence Fluckiger, pharmacist on the board of legal and regulatory affairs ANSM*
- *Dr Laeticia Gambotti, head of the INCa clinical research department*
- *Dr Marie-Line Garcia, head of medical pharmaco-vigilance within GERCOR (a multidisciplinary cooperative group in oncology)*
- *Dr Cécile Girault, director of the French-speaking federation of gastrointestinal cancers (FFCD)*
- *Mme Gaëlle Guyader, director of the authorization board at ANSM*
- *Dr Claire Labreveux, research and development director at Unicancer*
- *Dr Anne-Laure Martin, data partnerships director at Unicancer*
- *Dr Franck Morin, director of the French-speaking thoracic cancerology intergroup (IFCT)*
- *Mme Iris Pauporté, research delegate for the French cancer league*
- *Mme Isabelle Sainte-Marie, deputy director of the board of medicines 1 at ANSM*
- *Dr Stéphane Vignot, oncologist at the Jean Godinot cancer institute, medical innovation advisor for the board of authorizations at ANSM*
- *Dr Isabelle Yoldjian, director of the board of medicines 1 at ANSM*

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The Ethics and Cancer Committee
Founded in September 2008, the Ethics and Cancer Committee is an independent advisory board addressing all questions concerning ethics relating to cancer. Any person or legal body can appeal to them at any moment. The committee comprises 30 members coming from diverse backgrounds - healthcare professionals, patients' representatives, ex-patients or close relatives, researchers, lawyers, sociologists, philosophers, etc. The French Cancer League provides the functional means to the Ethics and Cancer Committee which chooses the themes it wishes to address before providing an independent opinion.
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