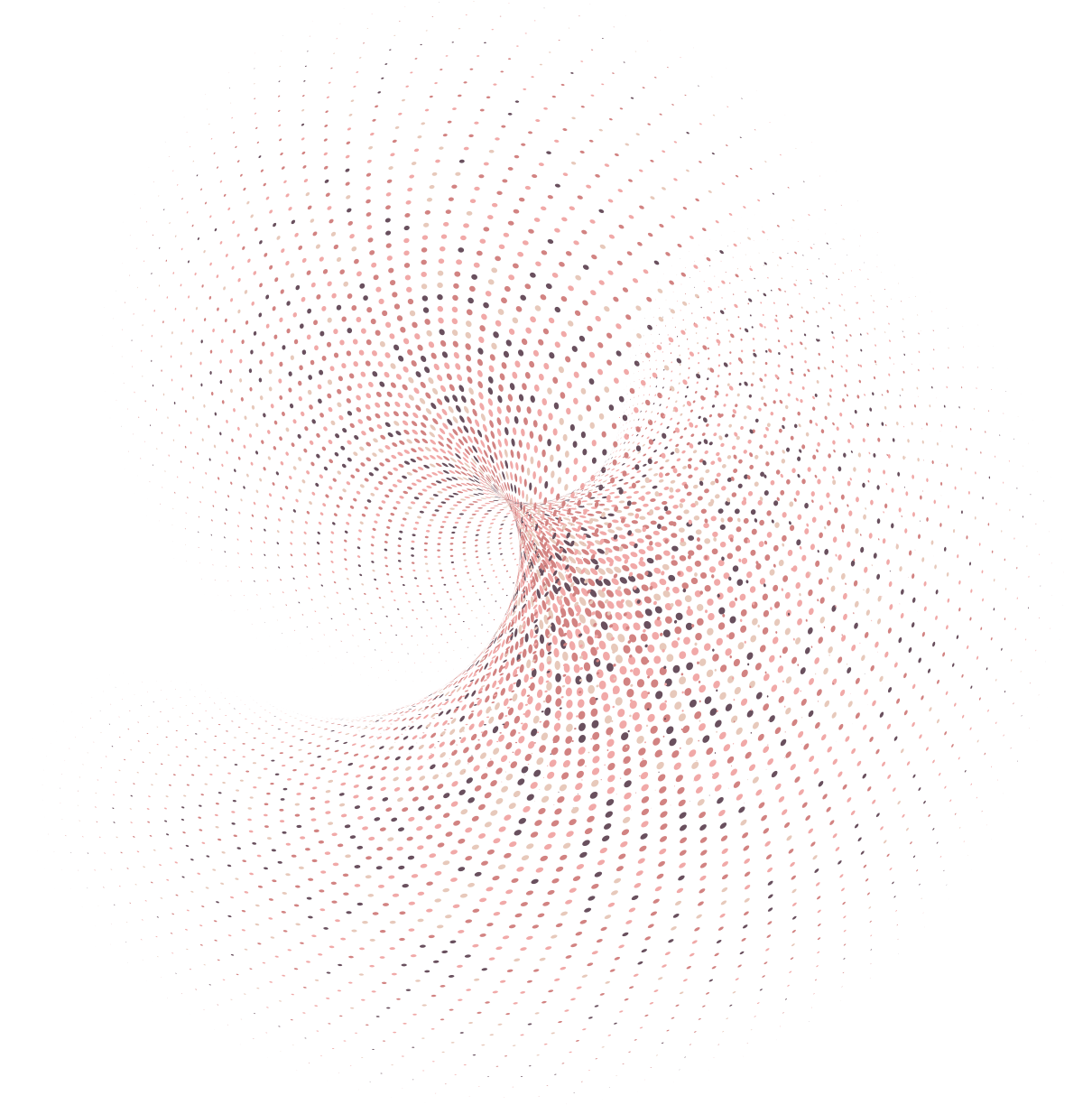
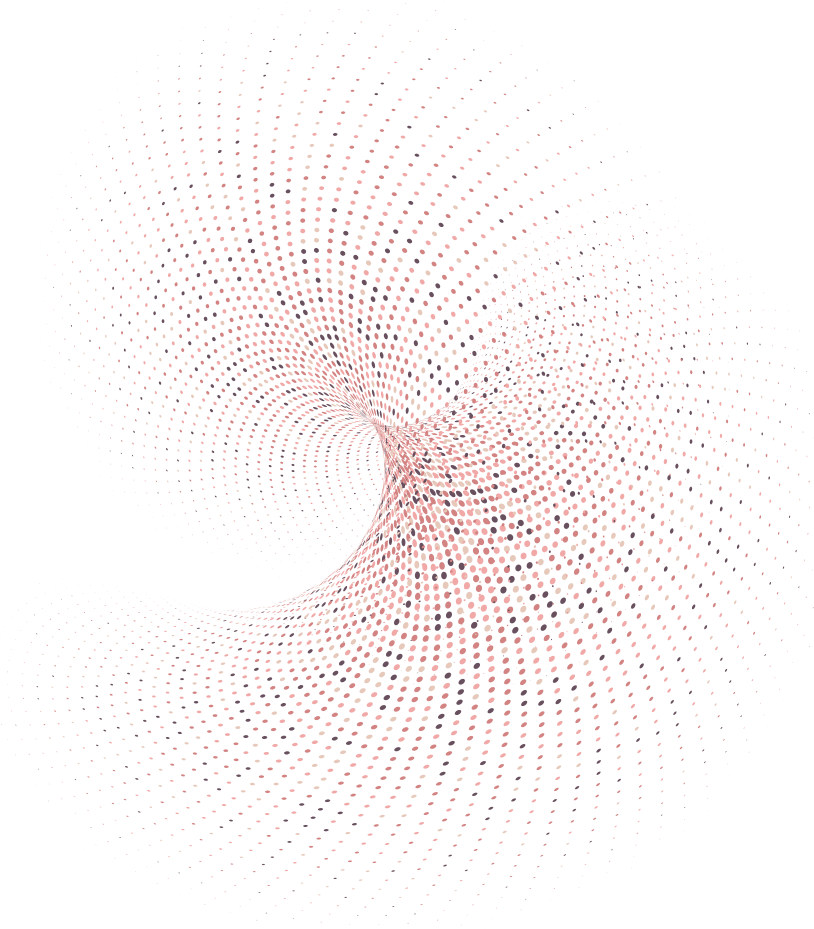
Naples Charter for the Protection of the Person in Clinical Trials





Naples Charter for the Protection of the Person in Clinical Trials

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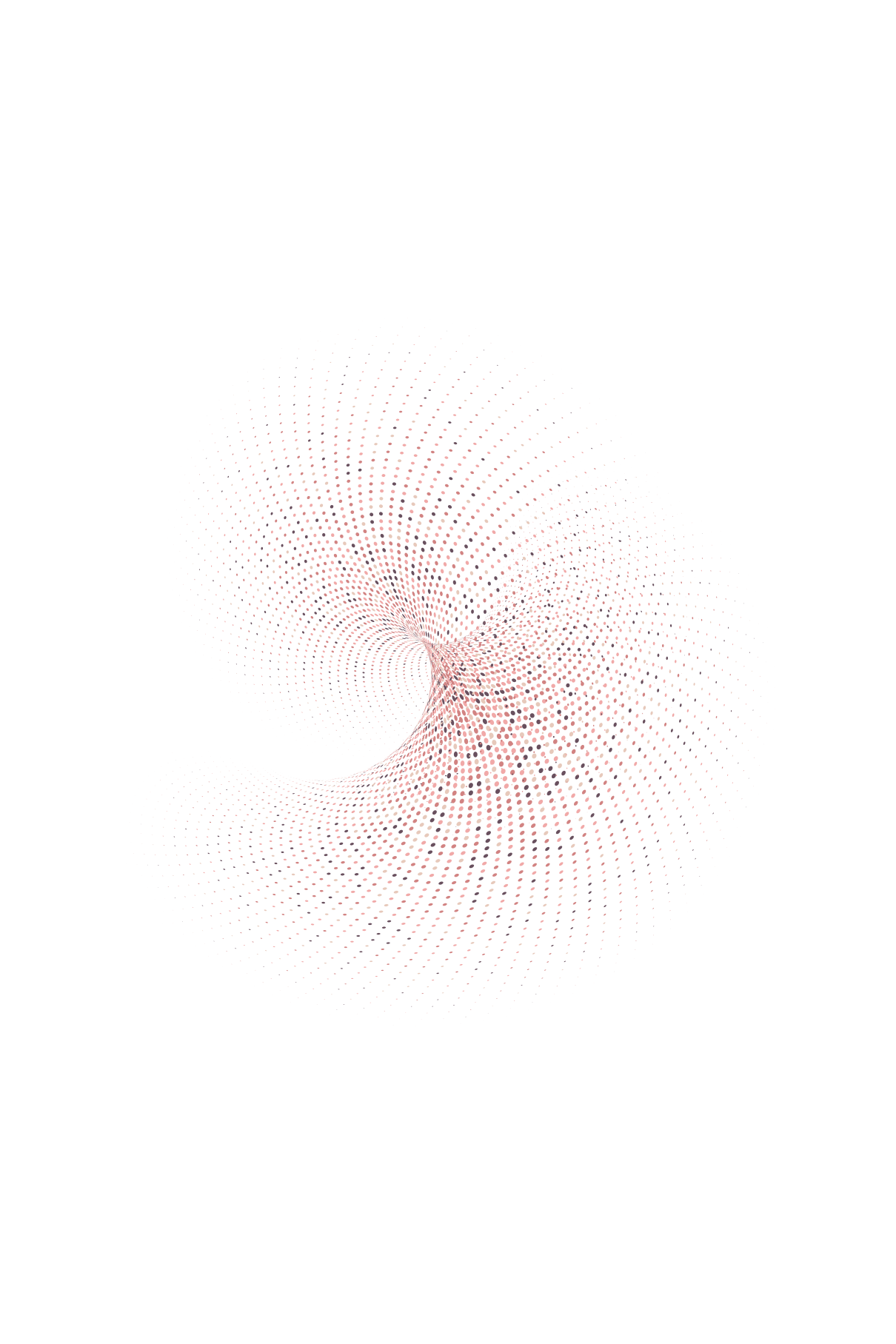

Preamble

1.- Why one more "Charter of Rights", especially in the matter of healthcare, where the production of such documents is far from being rare?

The hypothetical but predictable question does not seem to be out of place because, based on common experience, the need to draw up a "Charter" is especially felt in the absence of regulatory measures aimed at meeting certain needs felt by categories of citizens, and is meant to urge the legislator to bridge the gap.

This usual motivation for any "Charters of Rights" cannot be found in the specific field of clinical trials of drugs for human use, which the "Charter of Naples" refers to. That sector is not lacking regulatory provisions, but is rather regulated by copious and heterogeneous norms, which are not always easily coordinated and interpreted, because of their large number and lack of homogeneity.

What is then the need at basis of our decision to draw up this document?

The answer is twofold.

First, we feel a strong need to make a non-declamatory but rather operational contribution to the reaffirmation of the centrality of a principle governing the entire conceptual and functional system of clinical trials, and which therefore must be fully considered as the "center of gravity" of the same system. The reference is to the principle of the essential primacy of the protection of dignity and fundamental rights to self-determination, to safety, to the well-being and the confidentiality of the individual involved in clinical trials *over any other interest*. The principle is enunciated in prestigious ethical, deontological and legal documents[1]. As it is explained just below, the *Territorial Ethics Committees*[2] (hereinafter referred to as TECs) are recognized as guardians and guarantors of the compliance with that principle.

The need to emphasize the paramount importance of this rule emerges in a pressing way at a time, such as nowadays, when the propensity is felt to divert attention from this supreme principle, in order to polarize it on other certainly appreciable interests, but of a quite different importance. Among those other interests there is the increase of the competitiveness and attractiveness of our country in the highly sought field of internationally important clinical trials, also due to its substantial economic implications.

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[1] Suffice it to mention, for the time being, point 8 of the *Helsinki Declaration on ethical principles for medical research*, art. 2 of the *Oviedo Convention on Human Rights and Biomedicine*, Art. 3 of the *Additional Protocol to the Biomedical Research Act*, Art. 4 of the *Universal Declaration on Bioethics and Human Rights* of UNESCO, as well as, for Italy, art. 3 of Legislative Decree 6 November 2007, no. 200, art. 5 of the Decree of the Minister of Health of 8 February 2013 and Art. 3 of the applied policies attached to art. 47 of the current Code of Medical Deontology.

[2] This expression is technically more powerful than the traditional one ("Local Ethics Committees"), in line with the necessary regulatory anchoring of the competence of such committees to the territory (see Article 12, paragraph 10 (d) Law No 189 of 8 November 2012 that states that "each ethical committee is assigned a territorial competence of one or more provinces ...", see also the Motion of the National Committee for Bioethics of 25 September 2015, p.3, and the Opinion of the *Deontological Council* of the National Federation of Medical Doctors, Surgeons and Dentists of December 15, 2016, where there are no "Local Ethics Committees", but "Territorial Ethical Committees").

Hence the impending risk of putting those interests before the protection of the above-mentioned existential rights of persons participating in clinical trials. This risk is increased by the fact that silence on the aforementioned principle and approach to it, accompanies a harsh and sometimes jealous criticism of TECs, which are the bodies unanimously entrusted by the authoritative institutions, with the heavy but essential obligation to safeguard respect for the person's existential values, by guaranteeing their *protection in public*[3]. The above-mentioned documents were published by those same authorities. According to the opinion in question, the task should be taken away from these bodies, which "downgrading" or even *suppression* is proposed for, in order to give it to a *single* Ethical Committee[4].

If this were the case, it is not difficult to reach the disconcerting conclusion that such a "Single" Ethics Committee would have to take decisions on the ethical and scientific nature and feasibility of *all* clinical studies of Research Structures and hospitals on the *entire* national area, as a consequence it would be in the objective impossibility of fulfilling the unwaivable duty of ensuring the *concrete* and *effective* safeguarding of the fundamental rights of the people, who are motivated by a commendable sense of social solidarity to participate in clinical *trials* and take risks. It should also be considered that trials are always to be assessed with regard to the specific social and cultural environment where they are carried out.

If this is the paradoxical result, which would inevitably be reached, it is more than justified to ask who would benefit from such an aberrant situation.

2.- This disturbing prospect is in complete disagreement, not only with the sources mentioned above, but also with the choices made in our Constitution and in the Charter of Fundamental Rights of the European Union. Therefore really urgently the need arises to vigorously emphasize the *intangibility* of the dignity and the rights inherent to the person, with the consequent *need* of ensuring the protection of the individual *as a matter of priority*. Such protection, far from being downplayed by the latest legislation introduced by the European Union Regulation n. 536 of 2014, on clinical trials of medicinal products for human use, which the herein censored approach tries in vain to draw arguments in its own favor out of, is on the contrary further and precisely enhanced.

This Regulation, after stating in its "Whereas" that it is in line with the major international guideline documents on clinical trials (n. 80), and that it respects the fundamental rights and observes the principles recognized in particular by the Charter, and notably human dignity, the integrity of the person, the rights of the child, private and family life, the protection of personal data (83), in full accordance with its "Whereas" n.1, in Article 3, with the emblematic title of "*General Principle*", states

[3] So verbatim reads art. 2, first paragraph, letter. M., Of Legislative Decree 24 June 2003, no. 211, and art. 1 of Legislative Decree no. 200, and the Ministerial Decree of 8 February 2013, already mentioned.

[4] See, in this regard, the *Debate on Bioethics Committees*, at www.politeia-centrostudi.org, where there are also the critical arguments to that opinion.

that a clinical trial may be *conducted only* if: (a) the rights, safety, dignity and well-being of subjects *are protected and prevail over all other interests*; and (b) it is designed to generate reliable and robust data. Far from establishing the termination of the TECs, the supranational legislature further strengthens the principle and consolidates their existence in article 2, 2nd paragraph, n.11, where it confirms their *nature* and *function* without any reservation: "Ethics committee means an *Independent Body* established in a Member State in accordance with the *law of that Member State* and empowered to give opinions for the purposes of this Regulation."

3.- Once reiterated the *imperative* basic principle of the whole regulation of clinical trials and therefore the inadmissibility of reducing the relevance of and disempowering TECs all the way to suppressing them, which are tasked with ensuring its observance, with the adverse consequences above, the commitment, undertaken for this purpose in Naples on 22 October 2015[5], was fulfilled.

The Authors of the Charter, who rely on their many years of experience as chairpersons and members of TECs, decided to pursue a further objective by making the procedure even more functional, which is aimed at protecting the rights of the individual participating in clinical trials. In so doing, the reader is offered a second answer to the hypothetical issue raised in this *Preamble*. The Charter of Naples might play a *linking* role between the *abstractness* and *universality* of the norms regulating clinical trials, which are typical of any etheronomous source – including the rules of *Good Clinical Practice* – and the *concreteness and specificity* of the complex and multiform reality of clinical trials, upon which they are to act. The *concreteness and specificity* of the countless types of clinical trials cannot be ignored, if we want to safeguard the rights of the individuals participating in them. Such protection of rights does not rely on the mechanical application of certain conceptual paradigms – as it would be the case if the herein censored opinion were accepted –. It is rather based on an *analytical* and *effective* assessment of the particular subjective and objective situations where it is applied and of the type of trial. For this purpose, it became necessary to give a constant "extensive" interpretation of the rules dictated on this matter, always in full harmony with their *rationale*. Consequently, the statements enclosed in the "Charter" find their foundation and justification in those same rules. If this is the case, we can see a relation between the ones and the others – as they are converging towards a common purpose. Their relation is of both *complementarity* and *integration*, although with due consideration to the diversity of their nature and hence their cogency.

Of course, our lively aspiration to conduct this challenging but hopefully fruitful hermeneutic operation, without disorienting the reader, has obliged us to use a descriptive

[5] With the *Motion* unanimously endorsed by the Round Table on *Ethics Committee* by the title: *"What future? An invitation to the public debate"* (rapporteurs: Alfredo Anzani, Claudio Buccelli, Carmine Donisi, Silvio Garattini, Maurizio Mori, Lucio Romano and Antonio G. Spagnolo) within the 11th UNESCO World Conference on Bioethics, *Medical Ethics and Health Law*. This also accounts for the reason why the editors of the document called it "*Naples* Charter".

technique in line with a rigorous analytical and systematic criterion.

In so doing, our purpose is not formulating general and undifferentiated behavioral rules, but rather drawing attention first and foremost on the principles of information of any clinical trials. In the light of that, the reader is offered guidelines to overcome a few "critical" issues in the analysis of the specific subjective and objective profiles of the different types of clinical trials. This is the reason for the inevitably large number of "Paragraphs" the Charter consists of and "Sections" it is divided into – hopefully always written in an intelligible language.

4.- In conclusion, we would like to share some considerations.

The "Charter of Naples" is intended not only for people included in clinical studies, investigators, stakeholders, TECs research institutes, Patient Associations, but also State and regional Institutions responsible for the protection of health, Bioethics Research Institutions, Social Entities working in the field of biomedicine and the National Legislator. Subjects, who, differently and with different competences and responsibilities, pursue, among others, the aim of the *safety* of people undergoing medical treatments, and thus work to increase the spreading of the culture of *risk management*.

Indeed, just like the proposed *complementary* and *supplementary* function attributable to the "Charter", adherence to its statements could also contribute to an appropriate *risk management* in experimental trials. In trials, on the one hand, this takes on an emphasis far more significant than in the clinical practice, on the other hand, the value of patient *safety* is explicitly referred to by regulatory sources, as it was pointed out.

Hopefully authorities responsible for the standardization of clinical trials not only will pay attention to this document, but will also take it into account, in adapting the current law on the matter to that dictated by the aforementioned U.E. Regulation N. 536/2014 for the protection of the dignity and of the rights of the person, therein analytically and expressly defined as "*always* [...] *priority*" above all other interests.

Were this "Charter" to raise interest beyond national borders, it could be valued as an evidence of our country's lively sensibility to the protection and promotion of the existential values of the individual, even in the delicate sector of Clinical trials on medicines. The proper conduction of trials is entrusted to the development of a biomedical knowledge that is faithful to its *inalienable vocation*.

Finally, after what has been said above, it goes without saying that the sharing, of the operative choices highly desired by the researchers and entrusted to this document, presupposes the strict compliance of the specific juridical, ethical and deontological standards concerning clinical trials. Such standards are contained in international, supranational and national sources – some of which have been mentioned at the beginning. They are certainly known to the sector operators and therefore needless to be mentioned in the individual paragraphs, which draw inspiration from them, as noted above. Therefore, any derogation from this choice (see § 41), was introduced solely to make it easier for the reader to support.

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FIRST SECTION

GENERAL PRINCIPLES

§ 1 – Primacy of the rights of the person

In clinical trials, the dignity of the person and his/her inviolable rights to self-determination, security, well-being and confidentiality prevail over any other general and/or particular interest.

This cardinal principle is unanimously recognized on the ethical level and enunciated by prestigious, international, supranational, national, deontological and juridical sources.

§ 2 – Function of Territorial Ethics Committees [*] (TECs)

The same sources entrust the protection of the rights of the person mentioned in the previous paragraph with the Territorial Ethics Committees (hereinafter referred to as TECs). Members of TECs are also non-specialists, patients and representative of their Associations, who are required to provide public guarantee of this protection, and to assume the corresponding responsibilities.

§ 3 – Impartiality and independence of TECs

For TECs to carry out their essential function with great competence and in a third-party position, independently of research Structures, promoters, sponsors and researchers, it is necessary that

[*] See note 2 on the *Preamble*

their members are selected on the basis of proven cultural training and specific professional experience and appointed through suitable procedures, so as to ensure the achievement of the objectives above.

§ 4 – Characteristics and modes of information and consent for clinical trials

In order to ensure the freedom and awareness of the person – or of his/her legal representative – in manifesting "informed consent" to clinical trials, TECs verify that the "Information Sheet" to be submitted upon a preliminary interview with the examiner, is complete but not lengthy, and does not include "technical" terms and "jargon" expressions or suggestive statements, such as to diminish the description of the foreseeable risks and emphasize, on the other hand, that of the expected benefits.

TECs shall also ensure that the protocol lays down that the manifestation of consent in writing or, where appropriate, by means of audiovisual recordings or of other appropriate devices, takes place after a reasonable cooling-off period, with the assistance of trusted persons. However the correct understanding of the entire content of the above mentioned “Information Sheet” must be verified.

§ 5 – Effectiveness and efficacy of the safeguard of the person

In order to effectively and efficiently safeguard the rights of the person participating in clinical trials, TECs are located on the national territory in such a way as to ensure that evaluations of clinical trials are performed not in a general and abstract manner, but rather always with regard to the specific territorial reality and hence to the concrete

human, cultural, social, health, and economic contexts where they are conducted.

§ 6 – Multidisciplinarity and interdisciplinarity of TECs

Physiognomic characters of TECs are multidisciplinarity and interdisciplinarity. The first, relating to their structural profile, responds to the inevitable need for the opinions expressed on individual experimental protocols to be the result of not only biomedical and statistical evaluations, but also of psychological, ethical, deontological, juridical and economic ones. The second, inherent to their functional profile, is aimed at avoiding the risk of their "specialization", which could give rise to disparities similar to those attributable to the deplorable "fragmentation" of medical knowledge.

§ 7 – Duties of the members of TECs and of the Technical and Scientific Secretariats

The members of TECs and of the Technical and Scientific Secretariats undertake to take care of their professional updating, also by participating in initiatives planned for this purpose, to collaborate with each other in solving any problem arising in the performance of their respective functions, and to avoid situations of conflict of interest with sponsors and with researchers.

§ 8 – Inseparability of the scientific and ethical evaluation of clinical trials

Given the interdependence between the scientific nature of a clinical study and its ethics, TECs perform interdisciplinary

evaluations of the individual experimental protocols both from the scientific and the ethical point of view, and evaluate their importance for the community.

To this end, TECs always check preclinical data, if any, which the "rationale" of the study is based upon, and make sure that each protocol includes a systematic review of the state of the knowledge related to the treatment under investigation.

§ 9 – Relations between participants in experimental trials and TECs

Any person participating in a clinical trial has the right to contact his/her reference TEC at any time, to the end of obtaining further information and clarifications on the objectives and risks involved, the methods, the conduct, the duration, any substantive amendment to the original experimental design and the possible early closure of the trial.

§ 10 – Independence, autonomy and eligibility of researchers

For the purpose of protecting the inviolable rights of the person involved in experimental protocols, and in the interest of the community, TECs verify the independence and autonomy of the investigators, by analyzing the content of clinical trial contracts, and the absence of potential and / or current conflicts of interest.

In order to ascertain the suitability of the investigators, TECs evaluate the scientific and professional profiles of each member of the research *teams*.

Since they are required to perform their activity in line with high quality levels, researchers will keep up to date, also by attending courses as laid out in § 17.

§ 11 – Insurance against damage from clinical trials

With regard to insurance against any damage from clinical trials, that may be suffered by person participating in them, TECs, in addition to fulfilling the tasks assigned them by the applicable legislation, undertake to verify that among the information provided to the person is included also that on the most general policy conditions, and in particular that on the exclusion from the right to "compensation" and the termination thereof.

§ 12 – Patient Associations

It is necessary that Associations of patients without conflicts of interest express themselves on the determination of the priorities among clinical trials investigating pathologies in need of new or innovative treatments, within the competent bodies, and on the basis of criteria and procedures to be established.

§ 13 – National Institution with advisory function

When shared solutions need to be taken in case scientific and/or ethical, and/or legal problems of considerable complexity and of general importance emerging in the assessment of experimental

protocols with significant impacts on the protection of persons, reference TECs, in the person of their presidents, also by a collegiate meeting, are required to consult the National Support and Counseling Institution in the field of clinical trials, in the pursuit of shared solutions inspired by the principle of the primacy of the dignity and fundamental rights of the person.

§ 14 – Non-pharmacological clinical trials

Although the subject of this "Charter" is clinical trial of medicinal products, the principles outlined in the preceding paragraphs refer also to non-pharmacological clinical trials.

In relation to the following paragraphs, they are extensible to the above mentioned non-pharmacological clinical trials, consistently with the specificities and regulatory arrangements of the same.

SECOND SECTION

THE PROTECTION OF THE PERSON IN THE DIFFERENT TYPES OF CLINICAL TRIALS

§ 15 – Participation in clinical trials

For a conscious and weighted decision on his/her participation in a clinical trial, any person has the right to know first whether it is aimed solely at the acquisition of new biomedical knowledge (scientific trials) or if it is intended for the research of new preventive or diagnostic or therapeutic or rehabilitative treatments (the so-called, application trial).

§ 16 – Interventional and observational studies

It is the duty of TECs to ascertain whether the protocol under their examination should be included in the category of interventional or of observational studies, irrespective of the characteristics attributed to it by its sponsor or its investigators.

§ 17 – Independent clinical trials

In order to support independent clinical trials and to guarantee the people therein involved, once identified the source of the economic resources for conducting those studies, to the end of establishing their non-commercial nature TECs organize training and updating

courses for researchers, aimed at designing ethically and scientifically accurate clinical studies.

§ 18 – "Non inferiority"clinical trials

Given the serious reservations on the scientific and ethical level, reported by the majority literature regarding trials with a "non-inferiority design", it is one of the task of TECs' to check with particular care that the information to be given to the "enlistable" people are absolutely clear as to the purpose of the trial. The trial is not meant to confirm the superiority of the tested treatment, but rather to evaluate its margin of non-inferiority compared to the existing one.

Those trials should be designed so that any lesser benefit associated with the use of the new tested treatment is offset by other clinically relevant benefits for the patients and for the community, and evaluable in the same study.

TECs ensure that "non-inferiority" trials do not pursue solely marketing purposes.

§ 19 – *Placebo*-controlled clinical trials

One of the tasks of TECs' is to ensure that, in randomized clinical trials, control groups receive the best available treatment, including the right dose and treatment duration. Therefore, the use of *placebo* is justified when there are no therapies available. Only in special cases – carefully evaluated from the methodological and scientific point of view – it is possible to use *placebo* also when there is a reference treatment, provided that its use does not imply any additional risk to the person participating in the clinical trial.

TECs check that the reasons behind the decision to use the *placebo* in particular cases are clearly outlined in the "Information Sheet" for the patient.

§ 20 – Substantial amendments to protocols

In case of "substantial" amendments to protocols already approved, the reference TECs examine them with particular accuracy in order to ascertain their congruence with the original designs of their protocols. If this requirement is not fulfilled, the amendments cannot be approved.

§ 21 – Medical investigators, general practitioners and pediatricians

If general medical practitioners and/or pediatricians are members of the clinical trial team, TECs, in the priority interest of the person involved, provide the guarantee of their ability to undertake experimental activities by verifying their registration in the relevant Register kept and periodically updated by the Regional Authorities.

General practitioners and pediatricians – even if not registered in the Register – in case of participation of their patients in a clinical trial, and in order to better protect them, have the right and duty to obtain information from the investigators on developments in the trial and on the results achieved at its end.

§ 22 – Genetic clinical trials

With specific reference to genetic clinical trials – or trials involving

genetic testing –, TECs, when analyzing the risk/benefit ratio, consider all the risks from which damage may result to the person included in the study (and possibly for his/her blood relatives). These possible damages depend on the "sensitive" data, deriving from this type of studies.

§ 23 – Highly innovative clinical trials

The knowledge of the interaction of nanoparticles, stem cells and the most advanced immunologic, isotopic, and radiotherapeutic treatments with biological systems is still not exhaustive.Thus there is current uncertainty about the determination of their consequent risks. Therefore TECs must perform a particularly accurate evaluation of the relevant experimental protocols. They must pay specific attention to the correctness, comprehensibility and completeness of the information to be given to participants in those trials, in order to enable them to exercise their right of self-determination with necessary awareness and reflection.

§ 24 – Clinical trials in anesthesiology

In consideration of the strong emotional impact aroused in people who are candidates for general anesthetic treatments, testing of new relational and informative approaches to these interventions is desirable in order to make them less psychologically traumatic.

§ 25 – Clinical trials with hospitalized patients

When the person participating in the clinical trial is hospitalized

and his/her physician is also the investigator, before beginning the treatment, on the basis of the patient request, physician must inform him/her if the treatment refers to a drug utilized for his/her therapy or it is investigational.

§ 26 – Gender-specific clinical trials

In addition to the increase in the number of clinical trials for typically female pathologies and to the due cautions required by their conditions (see §§ 35, 36 and 37), women are entitled to broaden their participation in clinical trials for gender-independent pathologies. In that case, participation in each stage of the trials must be guaranteed, regardless of gender.

During the trial, participants are entitled to an accurate monitoring of their psychophysical conditions, taking into account gender differences both at pharmacokinetic and pharmacodynamic level, and concerning any other relevant aspect of the trial.

The analysis of the obtained data and results at the conclusion of the clinical trial shall be differentiated by gender.

During trials involving intersexual individuals, specialists are advised to pay particular attention to any interaction of the new treatment with their hormonal profile.

§ 27 – Clinical trials in procreative medicine

Recognizing the need for further investigation on the medium- and long-term side effects of the use of the various medically assisted reproductive techniques and to related pharmacological treatments,

the implementation of relevant clinical trial protocols becomes urgent, to the end of protecting women and their children not yet born, primarily upon the initiative of the Scientific Associations in that field of medicine.

§ 28 – Clinical trials in oncology

In consideration of the innovativeness of the drugs examined in oncological clinical trials, when evaluating them, it is the care of TECs to ensure that in the relevant protocols the utmost attention is paid to the principle of proportionality, the foreseeable risks, the duration and the quality of life of the "enrolled" person, in line with his/her existential choices.

§ 29 – Clinical trials for the purpose of human enhancement

Given the disparity of views in the scientific community on the eligibility of human enhancement treatments, when an opinion is requested on an experimental protocol for *human enhancement*, in addition to the physiological parameters of the human body, of the physical and/or mental capacities of healthy people, the President of the reference TEC, at the request of one or more of its members, promotes the drawing up of an opinion, including the possible intervention of external experts, as to the eligibility of the submitted study.

The general aspects of such opinion shall be kept into account also in the assessment of any future "enhancement" studies.

§ 30 – "Pilot" or "exploratory" clinical trials

It is expedient that TECs to conceptually identify the physiognomic characters of "pilot" or "exploratory" clinical trials possibly with the cooperation of the agency referred to in §13. TECs have the task of verifying in practice that there are all the right conditions to ensure adequate protection for the person participating in those trials, against the foreseeable greater risk to which he/she is exposed in this type of trials, taking into account the data available in the literature on the subject.

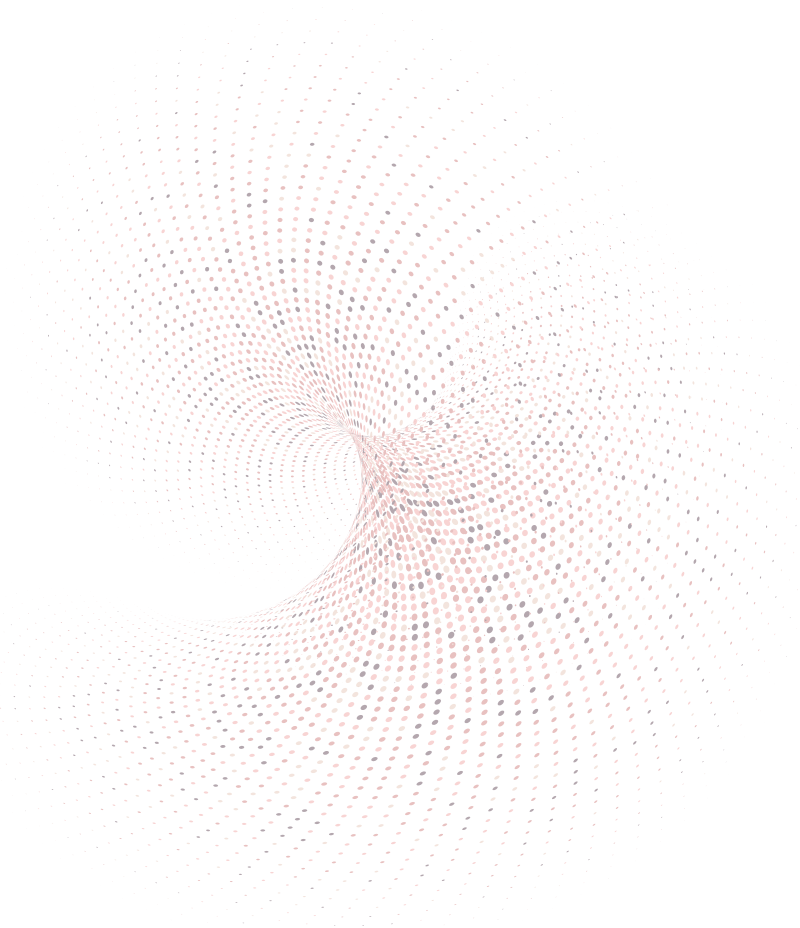
§ 31 – Phase-1 trials with healthy persons

Given the purpose of Phase-1 clinical trials, TECs evaluate with particular care the modes of participation of heathy subjects and the information to be provided them. Specific reference is made to the analytical description of the risks which participants would be exposed to, and to the measures to be taken to deal with them. All the above is meant to put them in the best conditions for an aware self-determination about their participation in the trial.

In order to safeguard the health of a healthy person to be included in a clinical trial, it is essential to create an international computerized system whereby to verify that the necessary period of time has elapsed between the conclusion of the previous trial and the beginning of his/her participation in a following one.

To the end of reducing the incidence area of the damage resulting from the possible toxicity of the treatment tested, this should be administered not simultaneously to all the participants in the trial,

but rather to each of them with appropriate time intervals between a treatment and the following one, and between a persons and another. This procedure is to be clearly described in the protocols and evaluated by the TECs of reference.



THIRD SECTION

PROTECTION OF "VULNERABLE" PERSON IN CLINICAL TRIALS

§ 32 – Clinical trials in pediatrics

On the consolidated assumption that children are not "miniature adults", it is urgent to increase the number of clinical trials on drugs specifically intended for them. Their purpose is to offer pediatricians a range of approved medicines, on the basis of pediatric population-based trials in the different stages of physiological development of preterms, newborns, newborns, infants, children, adolescents, with the consequent reduction of the risks associated with the use of off-label medications in clinical practice.

Without prejudice to the statutory powers of parents or of other legal representatives – who hopefully shall be adequately informed about pediatric research, and to whom researchers have to provide periodic accurate information on the progress of the ongoing trial – TECs shall verify that children with a sufficient degree of discernment, participating in clinical trials, are informed on the objectives and investigations provided for therein in a manner appropriate to their age and level of cognitive maturity.

§ 33 – Pediatric clinical trials with invasive procedures

In trials involving newborns, infants and children, where they are subjected to particularly invasive procedures – such as tracheal or esophageal intubation, colonoscopy, biopsies, lumbar punctures,

anorectal manometries – which may cause them psychic trauma and physical injuries, because of the size and fragility of their anatomical structures, TECs are committed to ascertaining whether those tests are indispensable for conducting the trial.

§ 34 – Clinical trials with pre-adolescents and adolescents with mental problems

In experimental protocols of psychopharmacological trials, involving pre-adolescents or adolescents with mental illnesses, the evaluation of TECs must be carried out with particular care on the composition of the teams of researchers, on the conduct and duration of the trials, given the possible interference of that category of medications with the cognitive development of the participants. In those cases, the presence of a psychologist of the development age is recommended.

§ 35 – Clinical trial with women of childbearing age or during pregnancy or lactation

Concerning women of childbearing age or during pregnancy or lactation, TECs are mandated to check that researchers give them and their partners exhaustive and comprehensible information on the risks associated with the clinical trial they are invited to participate, and related to a possible pregnancy, and to the newborn.The investigators give information about suitable measures to prevent unwanted events as effectively as possible and always respectful of personal ethical convictions of the person.

§ 36 – Clinical trials with pregnant women

When a clinical trail is required to be performed in pregnant women, since pregnancy has an effect on the absorption, metabolism and excretion of medicaments and medicines used during gestation are administered more on empirical basis than on specific scientific knowledge, it is the duty of the competent TECs to carry out an accurate assessment of the risk/benefit ratio for each protocol. Furthermore, TECs must ensure the performance of a systematic monitoring of the condition of the pregnant woman, of the foetus and of the newborn, after his/her birth.

Child monitoring should be continued for a reasonable period after the end of the trial, with the involvement of the adequately informed family pediatricians.

§ 37 – Clinical trials with menopausal women

When evaluating protocols for hormone treatments for the control of menopausal disorders, TECs shall ascertain that the drugs used in clinical trials designed for that purpose do not have an unfavorable risk/benefit ratio in relation to cardiological and oncological complications.

§ 38 – Clinical trials in psychiatry

When participating in clinical trials in psychiatry, the person has the right not to have drug combinations administered, whenever possible, and to be under constant medical supervision by the structure in which he/she is hospitalized or, if not hospitalized, by

the Departments of Mental Health, so that any adverse reactions can be addressed in a timely manner.

§ 39 – Advanced neurological clinical trials

As advanced neurological trials require the use of stem cells and genetic technologies, with consequent ethical and legal problems which are difficult to solve, there is urgent need for a confrontation between TECs, the Agency referred to in § 13, Patient Associations and representatives of regulatory Authorities, for the purpose of developing shared solutions.

§ 40 – Neuropsychiatric clinical trials and cooperation with attending physicians

Given the peculiar nature of the relationship between psychiatric or neurological patients and their attending physicians, the former have the right to to have the latter participating with the investigator when information is given on the experimental protocol and consent to participate in the trial is expressed or withheld.

§ 41 – Clinical trials with incapacitated persons and in emergency

Clinical trials with people who are incapacitated and with people in emergencies have raised such numerous and delicate questions as to induce the supranational legislator to include precise and detailed rules in the U.E. Regulation n. 586/2014 (Articles 31 and 35). It is the priority duty of TECs to ensure that those rules are properly interpreted and fully applied.

§ 42 – Clinical trials with persons with *locked-in syndrome*

Although the *locked-in syndrome* is not frequently diagnosed, special care requires the peculiar conditions of a person suffering from it, also in clinical trials.

Therefore, once ascertained the permanence of cognitive and volitional capacities, the person is entitled to receive all information about the proposed clinical trial and to express his/her decision to participate or not in it, by means of procedures and modalities considered suitable by the TEC of reference.

§ 43 – Clinical trials with old persons

The application to old persons of the results of experiments involving young adults raises quite a few criticalities. It is necessary to conduct a larger number of specific clinical trials exclusively for the elder persons, in particular for those with different pathologies and therefore subjected to more than one pharmacological therapy.

To protect their safety and well-being, competent TECs will ensure that the protocols provide in for an adequate program for monitoring their psychophysical condition.

§ 44 – Clinical trials with persons affected by rare diseases

Given that anyone who has the right to receive appropriate healthcare treatments whatever the nature of the disease he/she is affected by, TECs verify that experimental pharmacological protocols for rare and ultra-rare diseases are designed with the same scientific and ethical accuracy as used for other clinical trials. However, the

difficulty of recruiting participants, depending on the degree of rarity of the disease needs to be kept into account.

In order to increase the number of those trials, in addition to the committment of the Structures where they are carried out, the increase of necessary financial resources is also required, both allocated by public and private organizations, and contributed by citizens, following awareness-raising campaigns organized by the Ministry of Health, in agreement with the Regions and Patient Associations.

§ 45 – Clinical trials with patients in terminal stage

In trials with patients in terminal stage, their right to relief of suffering and to a dignified death must always be protected. Therefore, it is the task of TECs to ensure that the experimental team is supported by experts in palliative care and pain management, who can provide immediate assistance for them, throughout the duration of clinical trials.

§ 46 – Clinical trials with “fragile” persons

Also persons belonging to disadvantaged social groups and ethnic minorities are entitled to access clinical trials. TECs make sure that the information given them, for the purpose of a truly free, informed and aware consent, is provided in an appropriate manner and way and has always been understood with the help of cultural mediators, if necessary.

FOURTH SECTION

THE COMPLETION OF THE CLINICAL TRIALS AND PROTECTION OF THE PERSON

§ 47 – Right of the person to know the results of the clinical trial

At the conclusion of trials, their results, even if negative, shall be made publicly available, and participants in the trials have the right to contact the TECs of reference, if they feel that they have not had comprehensive and comprehensible information on their outcome. TECs endeavor to remedy to this dysfunction. At the end of randomized, controlled and blind clinical trials, the participants have also the right to be informed on the nature of the treatment received during the trials, where the design of the trial permits so.

§ 48 – Investigators and *mass-media*

In order to avoid creating possibly unfounded expectations in participants in clinical trials, it is ethically desirable for investigators to refrain from spreading news and releasing mass-media interviews on clinical trials that have not yet ended.

Upon their closure, the principle of transparency requires that they avoid publishing articles and releasing interviews containing data and results not – or not entirely – coincident with those indicated in the final report submitted to the Regulatory Authority.

TECs, in compliance with their competences and in the scope of their autonomy, as recognized by the current legislation, undertake to identify appropriate measures to make these behaviors effective.