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# Preliminary notes and remarks for preparation of a Code of Ethics for Health supporting Foundations

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## Foreward

The following considerations aim to discuss a number important ethical issues that emerge in the preparation of a Code of Ethics for Associations or Foundations dealing with problems related to human health, with special regard to Vascular Disease.

This article does not cover all possible issues appropriate for a Code of Ethics. Moreover, the opinions and suggestions expressed here do not necessary reflect the position of any particular Foundation.

Concepts and statements reported in this article only reflect opinions and choices of the Authors.

However, Authors recognize the inspiration received from VAS as essential for our approach to this work.

## Vision

1. Our main interest is directed to Vascular Disease (including Cardio- and Cerebro-vascular) as the major cause of mortality and disability in the developed world.
2. We however recognize the outstanding role of continuous general medical education.
3. We believe in the primacy of evidence based biomedical and clinical research as the best generator of medical knowledge and its translation to prevention and therapy of Vascular Disease.
4. In general we believe in a dynamic concept of scientific and medical knowledge, that can never be ultimate (even if evidence based), since it may ever undergo revision, adaptation, repositioning, and sometimes overturning by more advanced and comprehensive evidences.
5. However, we call for tolerance of some complementary cures as possible tools for improving quality of life, provided they are not alternative to evidence based therapies.
6. We strongly support the concept of freedom and responsibility of scientists and doctors but also of patients, as of any human being involved in the medical relationship.
7. We highly value communication and collaboration with any person in need of prevention or therapy, based on informed consent. The aim of "sharing" clinical decisions should however never transfer responsibility of care from doctor to patient.

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8. Finally, we also consider science (and in particular medicine), as a potent tool for pursuing understanding and collaboration among people of different age, ethnicity, culture, sex, gender, religion and socio-economic status.

**Mission**

The **Mission** of a Vascular Foundation, based on the above vision can be summarized as follows:

- Actions concerning advanced teaching and training in Vascular medicine to Medical and Technical graduates in Europe, aimed at forming experts in Vascular Medicine and related subjects.
- Actions directed to validation of career-oriented degrees (master degree, vascular specialty, vascular technicians, etc).
- Actions directed to fostering general medical education, in order to prevent hyper-technological fragmentation of medical skills and consequent detachment from the patient as a global human being.
- Support to European activities in the field of Angiology/Vascular Medicine, and specifically for the European Training Centers Accreditation, and for the European Exams.
- Authors encouraging prevention and early diagnosis also by promoting population awareness on vascular diseases and on healthy lifestyle.
- Actions directed to stimulate independent research as main choice of the Foundation.
- Actions aimed at defining and regulating "conflicts of interests" (COI) both economic and intellectual, and at enforcing corrective measures (disclosure, etc).
- Aim at supporting the development of clinical research, delivering clear concepts especially about randomized controlled trials (RCT), observational studies, and registries.
- Consideration of some ethical problems of RCT, as recruiting, blinding, randomization, correct adjudication of events, and presentation of results.
- Intention to better define the route from the "informed consent" towards management choices "shared" with the patient.
- Re-consideration of the role of statistics in planning and design of studies, as well as use and misuse of meta-trials and meta-analyses.
- Actions to suitably present and communicate probabilistic values and statistical data to patients and media, in order to avoid misunderstanding and distortion of data.
- Consideration of the cultural versus the practical role of guidelines and protocols, and their relationship with medical responsibility.
- Emphasizing the problems of information and communication: from doctors to the general population, and doctors to patients, media, health policy-makers and administrators.
- Networking with Institution, Associations and Scientific Societies with clearly defined goals, respecting mutual rules, and avoiding overlaps.

Some of these points are discussed in detail in the following pages.

**Considerations on Conflicts of interest**

We adopt with small changes the definition of "conflict of interests" proposed by the U.S. Institute of Medicine in 2009. **"Conflict of interest (COI) occurs when a set of circumstances creates a risk that professional judgement and actions regarding a prima-**

**ry interest will be unduly influenced by a secondary interest"** (1).

A conflict of interest may be either economic, (as for consultancies, fees, grants, gifts etc), or intellectual, as due to influences by factors as previous personal research; ethical, religious or political beliefs, affiliation to a certain school of thought, prevalence of career objective defense of personal/family social role, and others.

Thus, although most emerging conflicts of interest are of the pecuniary type, we should remind that economic interference is not the only form of COI, that should always be considered in a wider context.

We defend the principle that collaboration with pharmaceutical or medical device industry must not be considered "per se" detrimental (2). These relations might in fact produce not only negative, but also positive effects. The independent scientist may exert a beneficial influence on the counterpart (scientific or non-scientific) from the industry, thus positively influencing industrial decisions with advantages for the community (3). The scientist working in the industry may transfer to his independent counterpart a clearer vision of the degree of usefulness of scientific data in the real world.

Although this positive interaction occurs quite often, there exist a number of cases in which a merely commercial attitude can prevail, influencing most choices, as for instance choice of the background literature, design, plan of patient enrollment and selection, adjudication of endpoints, statistical evaluation, and sometimes even inducing withdrawal of negative results or advantageous alteration of their mode of expression and communication.

Should we then consider "a priori" that studies with exclusive or prevailing industrial support are of no value, presuming Authors to be usually biased because of COI? We do not adhere to this sort of "culture of suspicion".

Indeed, we do not support extreme positions, as for instance the claims that pretension reputation Journals should deny publication to studies entirely financed by the Industry (4).

We rather adhere to a more moderate attitude, favoring free judgement case by case (5,6), but at the same time enforcing strict criteria to evaluate validity, consistency, reliability and transparency of results.

An obsessive search for bias due to COI should be avoided: this behavior would increase the attitude that makes any relation with the industry, to be "per se" a proof that a scientific fraud is perpetrated "over the life of the sick" (7). The "anti-industrial prejudice" is highly noxious not only because it hampers development of new discoveries, but also because it may deviate thousands of patients towards "alternative" or "natural" therapies that have no scientific validation.

***Disclosure*** of COIs is an accepted practice that has our approval. Disclosure is indeed essential, although with some important limitations. In fact, although not accepting the definition of disclosure as a hypocritical practice (8), we should consider that this procedure may induce a false sense of relief, and may "thwart the principle that a work should be judged solely on his merits", thus deviating attention from the scientific quality of the study, and creating an "attribute substitution" (8).

Being conscious of this debate, we maintain that disclosure of competing interests, although being a procedure far from perfection, remains a sound and important practice: it is not a panacea for preventing COI, but certainly is a useful tool for limiting its effects.

However, while we confirm our preference for independent studies, when confronted with studies by Authors with probable COI we should try to go beyond disclosure, asking to experts to deeply evaluate the quality of

the study. Finally, we share in fact the conclusions of the "Consulta Cardiovascolare" (9), **that all researchers, independently upon their relations with industry, should have access and participation in any occasion of official scientific discussion, with equal dignity as those who do not have such relations**. In fact, absence of relations with industry is not always due to personal choice, but sometimes also to lack of opportunities.

Experts having steady or repeated contracts with industry should however not be attributed a leading or decisional role when essential (e.g. economic) problems related to drugs are discussed. This limitation is even more important when such experts are called to participate in committees producing guidelines or local protocols of medical practice.

## Considerations on Ethical Problems in Biomedical and Clinical Studies

Our attitude towards biomedical and clinical research in the vascular field is partly specified in the previous chapters. In fact, a Vascular Foundation should "Identify, promote and organize European research projects in the vascular field independently from any economic interest". However, in special conditions, participation in trials supported, in different forms, by public/private co-financing should not be excluded. Requesting and obtaining a patent for the Foundation when justified and appropriate is also not excluded. The constitution of National or Regional Agencies for Independent Research would establish an ideal counterpart favoring implementation of the above aims.

### *Biomedical investigations and animal experimentation*

A Foundation should be willing to offer free consultancy and, if necessary, assistance to any investigator, for planning and design of studies and validation of their results, after careful evaluation of the scientific and social value of the study.

A particular aspect of bio-medical, pre-clinical research is the debate about lawfulness of animal experimentation. The principles that forbid any gratuitous mishandling and violence towards animals should be accepted, but without accepting to attempts at demonizing and ban the practice of animal experimentation when justified and needed. In fact animal experimentation remains, at this time, an essential step in the evaluation of new drugs and innovative devices or procedures, prior to testing them in humans. Although not under-evaluating the inter-species differences, we maintain that testing in a complex organism cannot at the present time be substituted by any cellular or bio-molecular experimentation. Full attention must be given to respect of the current rules and laws about the due limits of animal experimentation and this should be openly declared in the protocol.

### *Clinical Investigations*

A Vascular Foundation should be ready to promote and culturally support clinical investigations, and mainly registries of patients, observational studies, and randomized clinical trials (RCT). Among the above, special attention is given to the development of registries as representative of the "real world" conditions.

### *Registries of patients* (RP)

The Foundation accept the principles and statements of the "Consulta delle Società Scientifiche per il Rischio Vascolare" (CCSV) (10), that can be summarized as follows:

**A Registry of Patients (RP) consists in a progressive collection of patients belong-**

**ing to a specific patient population, defined according to a particular disease, or risk factor(s), or treatment.**

RP patients are relatively unselected, thus reproducing as much is possible the features of the disease or of the treatment, as occurring in real life. Generally, RPs collect information without influencing in any way therapeutic choices that are decided by the responsible doctor rather than by the RP promoters.

RPs can be defined "cohort studies" if they collect a population of patients according to a certain property or condition as object of study, and measure along time predefined events or complications. The inclusion of a control group is desirable in any type of registry or derived observational study, and the evaluation of the different outcomes should when possible be prospective rather than retrospective.

Phase IV post-marketing studies differ from registry studies as being finalized to the evaluation of "on field" evaluation of use, advantages and side effects of a drug or device recently introduced in clinical practice.

RPs and observational studies have a limited number of ethical problems, as privacy, and utilization of personal data for goals external to the patients. Thus, approval of the RPs by an Ethical Committee and a document of informed consent signed by the patients are justified.

*Randomized Controlled Trials* (RCT)

RCTs are rightly considered the best tools for achieving dependable medical evidence.

However, after their first appearance in the fifties of 1900, RCT have been submitted to a continuing debate concerning a number of ethical aspects. Some early papers reporting reactions from reviewers and readers (11), had the impact of a "bombshell". They were determinant for the establishment of local Institutional Review Boards (IRB), and adoption of informed consent. Even at our days, some debate about ethics in RCTs is still open.

We mention here some of the arguments regarding these ethical problems.

- Reduction of the patient to a mere instrument used to obtain better knowledge, although in view of a future general advantage.
- In randomized double-blind studies, the value of informed consent has been questioned and even denied, and a condition of inferiority or discrimination of the control group versus the group treated with the study-drug or procedure has been claimed (12). On this background some experts of ethics suggest to adopt a number of tools of mitigation of the ethical impact of RCT, as:
- A wider use of data-bases, registries and observational studies as a preliminary background for RCTs.
- Immediate interruption of the RCT as early as it begins to show a positive difference between the investigational and the control group, meaning that the equipoise principle is infringed.
- Implementation of innovative and foundational statistical approaches directed to overcoming some conundrums, e.g. introducing a Bayesian approach instead of the more standard, and sometimes ethically problematic, frequentist one; or focusing on the limits of the p value and suggesting wider use of the confidence interval. The term "adaptive trials" has been introduced to define these approaches (13)
- Improvement of communication with the patient in order to make his acceptance of the study more solid.
- Limited use of placebo groups, favoring studies with a control group submitted to standard therapies or procedures.

Our position can be expressed as follows:

- In modern medicine, the margin of improvement that can be expected from a new drug or procedure is small, except for diseases for which no cure is available. Thus, a difference can generally be appreciated only applying rigorous statistical methods as randomization.
- Patients allocated in the control group are not discriminated: they will anyway receive the best available treatment according to the current scientific knowledge. Only if there is no validated cure they should receive a placebo.
- Conversely, the patient in the study group receives a treatment that might (hopefully) be better, but could also fail to show clinical superiority or be associated to more side-effects. Thus, the situation of the two groups is comparable as regards uncertainty.
- Elimination of the placebo and adoption of the best conventional treatment as control group offers a good solution, but might in some cases affect the power of the study, introducing new sources of variability.
- Less restrictive interpretation of figures indicating significance is not acceptable. $P < 0.05$ is already a weak statistical and often non-clinical significance (14).

At any rate we support the view to potentiate registries and observational studies, even if we agree that RCT remain necessary in order to obtain dependable data of efficacy in a reasonable time.

Finally, we are doubtful about the value of too many mega-trials, because of the great regulatory, geographic, social and lifestyle differences among Countries, that may affect all phases of the trial (15). We recommend for RCTs of reasonable size on patients selected for pre-defined characteristics.

*New corrective tools for RCT*

We observe with interest some modified models of RCT in which the usual randomized allocation is integrated by data originated from observational registries. These modified designs may lead to lower strength of outcome data, but provide better protection of patients (20).

Such "adaptive" designs are applicable both to exploratory and confirmatory studies. One procedure consists in making prospectively planned changes to an ongoing study, using the information obtained by continuous analysis of the results, either in a blinded or un-blinded manner. This methodology needs high statistical skills, but may allow to early identify, those patients who will most likely benefit from the study drug or procedure (13).

A new concept in this area is early **sharing of data** with other researchers, medical practitioners, and patients organizations. By this procedure, clinical researchers may be able to identify trends, or subpopulation effects leading to changes in global treatment guidelines and to evaluation and replication of clinical results, thus influencing research design and funding, although with a number of ethical issues (21). And advantages are foreseen by the impending availability of "big data", of which we can at this time imagine benefits, but also possible errors and surcharge of information.

Data sharing will involve problems of priority, consent, intellectual property, costs and infrastructures, that cannot be eliminated but only managed and mitigated (22). In order to avoid premature diffusion and utilization of trial results, control of data sharing should be attributed to ad hoc boards defined as Data Monitoring Committees (DMC).

These and other new modifications of RCT may answer to future problems of global (or globalized) health research (23).

*Meta-analyses: use and misuse*

Meta-analyses and similar procedures (e.g. network meta-analyses) are presently very popular, as they allow utilization of most of the published studies including those of smaller dimensions that would otherwise be neglected. Pooling of data is generally advantageous for statistical calculations. However, meta-analysis is a useful procedure especially when needed and feasible. Some biases in meta-analyses should be recalled, as heterogeneity of trials, publication bias, inclusion criteria bias, selection bias, time-related bias. The latter is often neglected: the results of similar trials can be very different according their timespan, due to changes in general health context, hygienic conditions, supportive treatments and nursing, dietary and lifestyle modifications, that can hardly undergo mathematical correction (15, 24).

First requirement is to accept results of meta-analyses that were really needed: e.g. when single trials with concordant results do not reach significance because of their small size. Meta-analysis of very discordant trials should be seen more cautiously because of possible in-homogeneity of trials and dilution of results by reiteration of data. Repeated meta-analyses based on similar trials with dubious or negative results are useless and confusing.

In conclusion, meta-analyses should be encouraged when the procedure is correctly indicated, applied and accomplished, but their results should always be considered with a cautious attitude.

*Informed consent*

We maintain that the consent of the patient in particular in its official form called "informed consent", is a necessary step for any type of clinical study, and is of outmost importance for randomized trials, blinded or un-blinded. Recently, some Authors recommend that the consent should not be "paternalistic", but should always be discussed and shared by the patient with his doctor. (16,17)

Information to the patients regarding gains and drawbacks of the study drug or procedure should be full and comprehensive. However, true sharing would mean total (i.e. also scientific) understanding by the patient, that seems to be an impractical demand. It is also important to avoid a transfer of responsibility from doctor to patient. This could be considered as an act of defensive medicine that is totally foreign to our vision.

*Role of statistics*

The role of the statisticians is essential not only in the evaluation and expression of result, but also much earlier, in building up plan and design, and following the development of the study. The mode of expression of data can make a difference for those who read and wish to understand and apply results of trials. For instance, a patient may prefer to hear that his disease has a 90% probability of healing rather than 10% probability of non-surviving. The problem of transmission of statistical data, as probability and risk, to patients and healthy persons, has been extensively treated by Kahnemann (18) who proposes the concept of "subjective probability", based on personal and familial experiences, a concept firstly introduced by an Italian mathematician (De Finetti, 19).

In conclusion, transmission to patients of concepts of statistical association, multiple causation, risk, and probability is induced a different task that may need the adoption of a new language.

*Guidelines*

Trials and meta-analyses are essential for the preparation of guidelines. We want to stress

that guidelines are not cogent tools that can be applied to any given case of a certain disease, but rather a cultural tools for the building up of knowledge about a given disease. Guidelines offer simply a cultural background that helps doctors in selecting the proper management in most, but not necessarily in all cases. Thus, guidelines in fact supply the necessary background information, but their literal application should not become a cogent duty, because every single case is a complex reality by itself. In consequence the mere fact that a guideline has not been partially or totally applied in a given case should not per se indicate a guilty conduct by the doctor (25). Despite these consideration, adherence to guidelines is currently considered a cogent duty and a decisive factor for charging professional guilt to health professionals.

It must also be noted that guidelines in great part formulated from evidence based data and notions.

However, we recall that scientific data are dynamic in nature and may change along time owing to different environmental and social factors. On the other hand, operational protocols issues by single institutions, only reflect the real conditions if applicability of guidelines in a given medical setting, thus presenting a validity that, being only local, cannot be applied to larger communities (e.g. to the entire Nation). The so called "Good Clinical Practices" are even less dependable and variable. For these reasons, guidelines are commonly used to evaluate clinical responsibility and guilty behavior, although this use appears inappropriate.

## Problems of communication and information

*Communication with patients*

The first rule should be that patients must to be treated as human beings in full possession of their own dignity. A relation of parity without any kind of paternalism should be established between doctors and patients. Only the general medical or surgical consultant, besides the family doctor, is entitled to transfer and "translate" to the patient clinical diagnosis, therapeutic choices and prognostic judgement. Specialty experts should limit their reports to information regarding their own area of competence and observation, avoiding general statements on diagnosis and prognosis. In this way, differences in definitions and options regarding the course of the disease will be avoided, and the patient will receive consistent and trustworthy information.

The patient should never be deceived about his state, even in case of severe prognosis. However, in these circumstances it is recommended to give first notice of such bad prognosis to a strict relative or partner, and plan with him/her a strategy for acting with consistency, delicacy and care. In case of disease of long duration and evolution it can be reasonable to give gradual information according to the current stage of the disease.

Specifications about duration of residual life expectancy should be avoided; in fact, such previsions, if later not confirmed, may seriously damage the reliability of the doctor and the patient's confidence. A grain of hope should always be left, as an attitude of fighting against the disease is conducive to better acceptance of these pies, even if palliative. All this unless the patient himself consciously asks to stop fighting.

We definitely are against perseverating and useless treatments and respect freedom of conscience in the frame of rules and laws about end of life, as in force in the different Countries.

Moreover, as responsible physicians, we always should remember that, while our evidence-based drugs and treatments are calibrated towards preventing hard events and

postponing death, many severely ill patients ask us primarily for relief from pain and misery, rather than for the gain of a few days or even weeks of life at any cost (26).

*Communicating the risk*

When informing the patient about the risk of a "hard" event, doctors should remember that probability is a statistical abstraction, difficult to be understood by the majority of patients. In fact, they will personalize the concept of a low probability (e.g. 1%) with a simple self-question: and what if that 1% happens to be myself?

Certainly, many factors may alter perception of risk. For example, although knowing that cardiovascular diseases are the first killing and invalidating condition, most patients will continue to fear much more the risk of cancer, whose image is accompanied by a series of episodes of suffering, misery, therapeutic impotence, or aggressive and noxious treatments (27).

The main causes of variability and biases in the individual perception of risk have been extensively described by Kahnemann (18). It is in fact very difficult to transfer crude statistical data to patients, as they very often modify interpretation of data on the basis of various of emotional and experimental factors (concept of subjective probability, 19).

*Sharing choices but not responsibility*

For all the above and many more reasons the current indication to share therapeutic or management decisions with patients, abandoning what is defined as the physician's "paternalism", is anyway a difficult task.

A realistic goal is to explain as clearly as possible benefits and shortcomings of any management choice, knowing that the patient is often more afraid of side-effects of effective drugs than of suffering due to refusing drugs. Some will in fact prefer to accept the so called "natural course" of the disease.

If the benefit clearly outweighs the shortcomings, the doctor could try to persuade (but not to manipulate), the patient, for instance by supplying more data and examples. But finally, the doctor must explicitly state his/her therapeutic opinion and accept the responsibility of a choice, which the patients is anyway free to refuse. In any case discussing and sharing medical choices with patients, does not mean sharing responsibility, that always remains only with the doctor.

*Communication between doctors and media*

In the present hyper-connected world, informing the media of advances in medical sciences and especially in medical or surgical therapies is a real need, that however implies dangers. We remind that the medical scientist should be aware that many if our "medical news" are minimal steps forward and that any scientific advance or even discovery is liable to be updated, altered, repositioned, and even denied by new evidence (28). This concept of "temporary and tentative validity" cannot be appreciated by the media that ask for "new discoveries", unequivocal statements, absolute truths, "breaking news". Medical scientists and doctors from one side, and the media on the other side, speak in fact incompatible languages. Only some journalists and reporters understand these differences and try to overcome the gap (29).

We recommend therefore all caregivers to try making media operators understand the concept that science usually proceeds with small steps, and that any scientific advance although dependable at the time, is also liable to dynamic modifications. Media operators should also be able to distinguish between hypotheses presented at Congresses (in which it may be relatively easy to read a communication), and evidence-based data from studies

accepted after peer review and published in medical journals of high reputation.

A cautious position should be taken about possible misuse of the social media of the Web, often diffusing unscientific notions. In fact, these media practice their own special language and are generally loose in controls. At any rate, the Web is presently deeply changing communication between doctor and patient (30) and this reality should not be ignored, but if possible faced with an appropriate language.

*Communication with public health officers*

Our position consists in making available to health officers the best updated scientific outcomes, clearly indicating benefits, risks and shortcomings of new drugs or procedures, without concealing the dynamic nature of any scientific truth.

Among the goals of a Foundation, the function of monitoring deliberations of national or regional bodies, should be fulfilled, with the aim to ensure their adherence to principles of socio-economic equity, especially relevant in case of new drugs or treatments. This kind of monitoring includes also enforcement of objectives of prevention and rehabilitation, that are often neglected by regulatory bodies. More generally, the Foundation is committed to identify and suggest to health authorities new projects and initiatives capable of improving health and wellness of people also in human, social and economic terms. At this regards, different keywords or key sentences may be proposed, indicating clear objectives, as for instance: "No more vascular amputations", an effective slogan leading to optimize monitoring and treatment of Peripheral Arterial Disease (PAD). In particular the Foundation should submit to Health Authorities projects finalized to privilege non-pharmacologic prophylaxis of vascular disease, based on life-style changes and psychological approaches. Obviously, explaining recourse to drugs and endovascular or surgical procedures, whether and when necessary, remains among our fundamental tasks.

*Medical and Health Education*

The Foundation should consider pre-, post-graduate, and continuous medical education, as well as health education in general, as a major task. Educational activities should cover all aspects of (Vascular) Medicine including Pathology, and Clinical, Instrumental and Imaging diagnosis, Blood Coagulation and Thrombosis, Clinical pharmacology and Toxycology, Interventional and surgical vascular procedures and also basic principles of vascular prevention .

Educational programs as Courses addressed to the above subjects will be proposed, with the collaboration of internationally recognized experts. All components of the Teaching Faculties, are expected to operate "pro-bono".

*Participation of Industry in teaching activities*

The financial burden of any educational event of a Foundation should mainly weigh down on its own resources. Direct funding of the Course from the pharmaceutical or medical device industry must be avoided. The Foundation can however receive funds for general educational activities from any public or private source, including the industry, in form of a declared "unconditioned contribution to medical and health education activities", preferably not directed to a specific event. None of these private sources of funds can ever interfere in the scientific program, that is unique responsibility of the Foundation Committees. Private contributors can be quoted and recognized in the Course

program, but stands or booths of pharma or device companies will not be permitted, and sponsored lectures will not be accepted.

However, the participation of doctors and researchers from the industry as auditors and discussants, is highly encouraged and welcomed, provided they previously declare their disclosure of interests.

*Fostering Awareness, and collaboration with other bodies*

Awareness is an important part of Education that consists in a daily, continuing activity of minute information on the main problems of prevention, early diagnosis and treatment of vascular disease. The Foundation will organize dedicated meetings, for presentation of results obtained in terms of awareness to other scientific and social organizations. In fact the activities will include multilevel collaboration with medical and social bodies favoring integration and avoiding overlapping of objectives. Exchange of information and promotion synergies collecting different initiatives and projects directed to the fight against vascular diseases.

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**References**

1. Lo B, Field MJ. Conflict of interest in medical research, education and practice. National Academies Press (US), Washington DC, 2009.
2. O'Donoghue M.L. Are all relationships with industry inherently bad? Medscape. May 25, 2016.
3. Drazen J.M., Harrington D.P., McMurray J.J.V. et al. Academic, Foundation, and Industry collaboration in finding new therapies. N Engl J Med 2017; 376: 1762-1979.
4. Steinbrook R, Kassirer J.P., Angell M. Justifying conflicts of interest in medical journals: a very bad idea. BMJ 2015; 350: h2942.
5. Drazen J.M. Revisiting the commercial-academic interface. N Engl J Med 2015; 372: 1853-1854.
6. Lüscher T.F. Conflicts of interest and the truth of scientific discovery: an editor's perspective. European Heart Journal 2016; 37: 738-740.
7. Ross J.S., Krumholz H.M. Conflicts of interest, authorship, and disclosures in industry-related scientific publications. Mayo Clin Proc 2010; 85(2): 199-200.
8. Rothman K.J. Conflict of interest. The new McCarthyism in Science. JAMA 1993; 269(21): 2782-2784.
9. Poli A. Conflitti di interesse in ambito Cardiovascolare: la posizione della Consulta. www.consulta-cscv.it June 15, 2016
10. Palareti G. Registri di pazienti (RP) Sanità Sole 24 Ore Supplemento 26 luglio 2016
11. Jones D.S., Grady C., Lederer S.E. Ethics and clinical research. The 50th anniversary of Beecher's bombshell. N Engl J Med 2016; 364: 2393-2398.
12. Parere del Comitato Etico. Orientamenti sull'utilizzo della randomizzazione nella sperimentazione clinica. I quaderni della Fondazione Umberto Veronesi, 2014
13. Bhatt D.L., Mehta C. Adaptive designs for clinical trials. N Engl J Med 2016; 375: 65-74.
14. Zhu W. $p<0.05$, $<0.01$, $<0.001$, $<0.0001$….. Journal for Sport and Health Science 2016, 5: 77-79.
15. Yusuf S, Wittes J. Interpreting geographic variations in results of randomized,

controlled trials. N Engl J Med 2016; 375: 2263-71.
16. Boniolo G., Di Fiore P.P., Pece S. Trusted consent and research biobanks: towards a "new alliance" between researchers and donors. Bioethics 2012; 26: 93-100.
17. Grady C., Cummings S.R., Rowbotham M.C. et al. Informed Consent. N Engl J Med 2017; 376: 856-867.
18. Kahnemann D. Thinking fast and slow. Farrar, Straus and Giroux p 499. New York 2011 ISBN 978-0374275631.
19. De Finetti B. Sul significato soggettivo della probabilità. In Fundamenta Mathematicae, Warszawa. T. XVII, pp 298-329, 1931.
20. Fiore L.D, Lavori P.W. Integrating randomized comparative effectiveness research with patient care. N Engl J Med 2016; 374: 2152-2158.
21. Bull S., Roberts N, Parker M. Views of ethical best practices in sharing individual-level data from medical and public health research: a systematic scoping review. J Empir Res Hum Ethics 2015; 10: 225-38.
22. Drazen J.M., Morrissey S., Malina D. et al. The importance – and the complexities – of data sharing. N Engl J Med 2016; 12: 1182-1183.
23. Bothwell L.E., Greene J.A., Podolsky S.H. et al. Assessing the gold standard – Lessons from the history of RCTs. N Engl J Med 2015; 374: 2175-2181.
24. Bailar J.C. III. The promise and problems of meta-analysis. New Engl J Med 1997; 337: 559-560
25. Schünemann H.J, Al-Ansary L.A., Forland F. et al. Guidelines international network: principles for disclosure of interests and management of conflicts in guidelines. Ann Intern Med 2015; 163: 548-553.
26. Hartzband P., Groopmann J. There is more to life than death. N Engl J Med 2012; 376: 987-989.
27. Rosenbaum L. "Misfearing" – Culture, identity and our perceptions of health risks. N Engl J Med 2014; 370: 595-597.
28. Prasad V.K., Cifu A.S. Ending medical reversal. John Hopkins University Press, 2015.
29. Hartzband P., Groopmann J. The new language of medicine. New Engl J Med 2011, 365: 1372-1373.
30. Hartzband P., Groopman J. Untangling the Web. Patients, Doctors, and the Internet. N Engl J Med 362; 12: 1063-1066.