



GOOD SCIENTIFIC PRACTICE (GSP) AND GOOD CLINICAL PRACTICE (GCP)





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Intellectual dishonesty in science

KEYWORDS: Professional ethics; Scientific misconduct; Fraud

Morals define rules of human behavior imposed by religious or political bodies and vary according to different traditions, cultures and interests. Hence, morals of some may be dangerous for others. Ethics is a minimum moral sense, provided by scientific knowledge, with the optimum means of survival for all (1). In such a way, science has broadest ethical character.

The main goal of science is truth based on scientific methods and honesty of scientists. That is why the biological scientists of twentieth century have believed that use of powerful scientific methods and modern techniques will diminish bias and improve objectivity of their work and protect their studies from errors and misleading conclusions. But, since these methods cannot protect scientists from errors in planning and conducting experiments and biased selection in reporting results, scientific objectivity must be based on the canons of ethics. Thus, any violation of ethical norms in science represents a case of intellectual dishonesty.

Many forms of intellectual dishonesty in medicine, particularly different errors in both clinical and scientific research, are inevitable. They originated in the past and will exist as long as human beings are doing experiments and clinical practice. Fortunately, although we would expect a greater number of cases of intellectual dishonesty (more scientists, more publications), there is no evidence of an increased rate. More than 99.9 percent of reports are accurate and truthful. The number of cases of intellectual dishonesty is smaller in science than in other fields (2).

Definition. The widest definition involves all forms of intellectual dishonesty, from common (honest) errors or errors due to carelessness to the most serious ones such as fabrication of data (fraud). The narrow definition defines fraud as "fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting research results" (3).

Forms. Intellectual dishonesty in science may be divided in different forms. Zuckerman (4) described the concept of "reputable and disreputable errors in science". Reputable errors are the unavoidable hazards of research of prevailing methodological nature. Disreputable errors result from violation of both methodological and ethical norms of science.

The importance of intention has been pointed out by Engler et al. (5) who distinguish: *mistakes* - cases in which the scientists had no knowledge that the statements made were incorrect; *careless errors* - cases of errors in which

scientists had no intent to deceive; *fraud* - cases in which author(s) made statements that are intended to induce others to believe things that are known to be false.

According to Lock (6), there is a whole gradation of intellectual dishonesty in science, ranging from common, honest errors, through bias and false interest, to fabrication of results - fraud being the most extreme case (Table 1).

Table 1. Gradation of intellectual dishonesty in science

Good faith	"Trimming", "cooking"	Fraud
Wrong observations	Manipulating data	Piracy
Wrong analysis	Suppressing inconvenient facts	Plagiarism
Wrong references		Forgery
Bias		
Self-delusion		
	Gift authorship	
	Duplicate publication	Undeclared interest
	Salami publication	

Most forms of intellectual dishonesty, their causes, famous affairs, preventive measures and sanctions are described in detail elsewhere (7). Here, only the main characteristics are mentioned.

Honest errors or errors in good faith are a part of scientific research and even with the best effort, no scientist can be certain of having avoided them. The majority (errors in numerical values, inconsistency of numbers in table with those in text or with previously published results, wrong references) are produced due to carelessness or haste.

Bias and self-delusion are difficult to exclude even though it is well known that scientists are supposed to be honest and modest.

Gift (honorary, false) authorship is the custom of including laboratory (department) directors' names on all papers produced in an institution. Such persons listed as authors usually are not directly responsible for the intellectual content of a paper. This approach tends to corrode responsibility and weaken the integrity of science.

Multiple (parallel, repetitive) publications of the same data are described in more detail elsewhere (8).

Salami publications represent the slicing of one study into a series of usually minor papers.

Fraud is the most serious or extreme form of intellectual dishonesty in science. The most common forms of fraud are piracy, plagiarism and falsification or fabrication of data.

Well-known affairs. *Dr. John Darsee* (9), as an author or coauthor (18 full-length research papers and about 100 abstracts published in major biomedical journals over a period of about three years), was detected (1981) falsifying data in laboratory studies at Harvard and elsewhere. Three investigating committees found that he had fabricated much of the data in his over 100 publications. Nearly all papers and abstracts contained errors and minor or major discrepancies. All publications were formally retracted.

Dr. Robert Slutsky (5), University of California, San Diego, while engaged in research in cardiology, nuclear medicine and radiology (1978-1985), was the author/co-author of 137 articles. Of these, 77 were classified as valid, 48 as questionable and 12 as fraudulent. Slutsky was producing one article every 10 days. The investigation found reports of experiments and measurements that had never been done, incorrect procedures and reports of statistical analyses that had never been performed.

Cause. It is agreed that the major causes of intellectual dishonesty in science, and of fraud in particular, are (5, 6, 10): individual aberration and personal motives; the pressure for newness at all costs (the race for priority); publish or perish syndrome; equation of excellence with quantity (publication number) rather than quality; competition for scientist grants, promotions, tenured positions etc.

Measures. Any system dealing with intellectual dishonesty in science can never eliminate its occasional appearance, but the scientific community itself can do much to minimize the incidence of such cases and facilitate their detection (6, 10). All forms of intellectual dishonesty are unacceptable in sci-

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entific work and science must be free of them.

Prevention is the best measure, and the pivotal role belongs to scientific institutions. The effort of institutions must make biomedical research free not only of fraud but of errors as well. A set of guidelines has been established: a scientist must always examine the results of colleagues with a healthy skepticism (reproducibility of the results); the scientist should cultivate an ethical atmosphere that will encourage young researchers to uphold the tradition of trust and to teach them in good scientific (laboratory) and clinical practice; working data books (primary data) must be kept at the institution for several years; each institute must have a body (formed not on an *ad hoc* basis) and procedures for investigating suspected intellectual dishonesty (ethical committee, ombudsman etc.); elimination of the publish or perish syndrome (foster quality over quantity, e.g. limit the number of publications reviewed for research grants, faculty appointments or promotion) (11); editors and referees must pay more attention to suspicious elements (excessive number of authors, data that are inconsistent, duplicate publications, salami publications, failure to acknowledge others or misleading citations) in manuscripts submitted for publication.

The sanctions for any form of intellectual dishonesty, whether committed in good faith or otherwise, are very severe: the loss of scientific credibility and career in science. Published articles with detected intellectual dishonesty must be retracted from the journals concerned and from bibliographical databases.

The impact factor. Data on the impact of intellectual dishonesty in research on the scientific literature do not exist (12).

In our literature there are no systematic data about intellectual dishonesty in science. But, the existence of different forms of intellectual dishonesty may be assumed given insufficient use of the scientific method, erosion of morals and a lack of appropriate guidelines in our milieu. Honorary authorship, salami publications, multiple publications and violation of copyright are among the most frequent.

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Safeguarding Good Scientific Practice

The experiences of Yugoslavia and other European countries

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The broad discussion on the need for new regulations to protect science and scientists against abusive research policies resulted in wide acceptance of the proposals and recommendations formulated by the International Commission on Professional Self-Regulation in Science (1). These recommendations are addressed to all institutions of science - universities and independent research institutes, learned societies, scientific journals and funding organizations - with the main aim to initiate, develop and implement a consciousness of good scientific practice in their day-to-day activities. In order to be effective, the good scientific practices have to be made explicit in written guidelines or codes (2).

The Proposals have been met with a great success: a number of countries that had not done it before adjoined this Pan-European initiative. In these countries, many institutions of science have formulated and implemented the rules of the professional conduct of science (3). Other European institutions of science are increasingly introducing these measures (4).

However, the European Science Foundation (ESF) insists that such ethical codes have to be more widely adopted by all European universities and research institutions, observed by all researchers and monitored for compliance. The ESF is uniquely placed to play a significant role in promoting the highest levels of scientific integrity and better self-regulation across Europe. Moreover, ESF stresses the need to extend and harmonize codes of good scientific practice in inter-organizational and international collaborations (5).

To achieve this goal, ESF calls for close partnership with other European organizations representing institutions of science; meanwhile, ESF encourages all scientists to promote the principles of GSP whenever possible.

Situation in Yugoslavia. Unlike the situation discussed at this very site a year ago (6), several ongoing actions of our scientific community have already given certain results. After broad discussions amongst their academic staff, two Yugoslav research institutes - Institute for Oncology and Radiology of Serbia and Institute for Medical Research - have formulated the rules of good scientific practice and complementary procedures for investigating allegations of the scientific misconduct (7,8).

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The editors of two scientific journals - *Archive of Oncology* and *Bulletin of Hematology* - after publishing several Editorials on this topic, have clearly stated that they are committed to the best international practice with regard to the publication ethics (9,10).

Learned societies such as the Yugoslav Society of Immunology and Medical Academy of the Serbian Medical Association have organized lectures related to their obligations concerning professional ethics.

Future directions. The above research institutes constantly promote the principles of good scientific practice in various ways - by lecturing at scientific meetings, publishing articles related to this topic, and initiating discussion in the wider scientific community. Actually, the authors of the above-mentioned ethical codes are trying to provoke our main funding agency, the Republic of Serbia's Ministry of Science, Technologies and Development, to set out their own rules; these should specify legal relationships between the Ministry and the grantees. The Ministry should also oblige its reviewers to adhere to the principles of best international practices when evaluating the science and the scientists.

Since the European Science Organization "acts as a catalyst for the development of science by bringing together leading scientists and funding agencies to debate, plan and implement pan-European initiatives" (5), it is of special interest for our country to become a member of this organization. Our Ministry of Science is expected to take the necessary steps in order to achieve this goal. Meanwhile, all members of our scientific community are expected to adopt the highest standards in the conduct of their research, to ensure that high ethical principles of science are achieved in practice, and to increase the awareness of good scientific practices in their surroundings.

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Good scientific practice in research funding organizations

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Research funding differs in modalities between countries and may involve support of particular research projects through governmental funding, independent foundations or funding agencies. In USA most of the research programs are supported through the National Science Foundation (NSF), National Institutes of Health (NIH), Fogarty foundation and a number of intramurally funded research projects at universities and institutes. In United Kingdom seven research councils are formed covering different fields of scientific work and powerful private foundations like Wellcome Trust, Leukemia Research Found, and others. In the rest of Europe, the countries are mostly oriented to the basic national support of science through ministries for science or related funding organizations. Recently, the European Science Foundation (ESF) was formed to promote cooperative approach and harmonization in scientific practice (1).

Good scientific practice (GSP) in research and education is the fundament for international integrity of science. The globalization of economy and culture prompted extensive inter-organizational and international collaborations in science. Therefore, harmonization in the principles of good scientific practice appears to be essential at the level of not only moral issues and ethics, but also in more practical procedures throughout the research and publishing process. Education and responsibility of an individual researcher is the basis for GSP but the scientific work today is not an individual issue and accordingly, research institutions and funding organizations or research communities in general are responsible for the promotion of the standards of GSP (2). It is therefore recommended (and already implemented by several countries) that funding organizations issue guidelines on the requirements for project applications incorporating statements on GSP (3). This prompted several research institutes and universities to proclaim their own GSP principles oriented mainly to the aspects of practical work and ethic principles. Other approaches involve formulating the obligatory principles for conducting basic research, clinical research, laboratory practice, manufactory practice and ethical principles in the use of laboratory animals. The GSP is therefore a part of standards defined at the legal level for a number of activities and products.

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It is important for both the individual researcher and institution, as well as for funding organizations, to comply with the same GSP standards. At the level of application for a project proposal previous work and other relevant information should be pointed out. The principal investigator and his institution should state that they adhere to GSP. At the level of the funding organization confidential peer review and elimination of potential conflicts of interest are essential. It may be useful to introduce an independent committee or a person in the capacity of Ombudsman. As a person of confidence, the Ombudsman advises scientists and institutions on GSP principles and responsibilities related to application, processing and reviewing of the projects as well as on the further realization of research programs. This enables research funding organizations to promote high standards and scientific integrity. They oblige institutions and principal investigators to work according to the standards of GSP. On the other hand, it is possible to require of research institutions to formulate their own rules of GSP.

The leadership of funding organizations and responsibility for continuous scientific work leading to possible development in practical issues needs transparency. In practice, this means written requirements and procedures including the criteria for peer review of the projects and administrative responsibilities.

In Serbia, there is an initial level of proposing the GSP criteria put forward by enthusiastic scientists at the Institute for Oncology and Radiology of Serbia and Institute for Medical Research, Belgrade. Both institutions accepted coordinated GSP principles (4,5). However, it seems essential for the Ministry of Science, Technologies and Development as the principal funding organization in Serbia to declare essential GSP standards as obligatory for the funded research programs. Last year, the European Commission adapted a policy paper "Towards a European research area" proposing stronger links between ethics committees at national and European levels to achieve more uniform standards of GSP in Europe. National institutions in cooperation with the Ministry for Science, Technologies and Development are well placed for leadership in promoting scientific integrity and good standards.

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Good scientific practice in research institutes - responsibilities of heads

KEYWORDS: Good scientific practice; Research institutes; Authorities

Good practices, including good scientific practice, nurture trust within the scientific community and between science and society, both of which are necessary for scientific advance (1). On the other hand, good scientific practice is essential for the integrity of science, improves quality assurance, strengthens the self-regulation of science and reinforces public trust in science (2). Institutions of science - independent research institutes together with universities, as the places where all scientific activities, such as experimental work, discussions, exchange of knowledge, writing, learning, are held, are essential for both formulation and approval of rules of good scientific practice.

In accordance with its statutory mission, institutions are responsible for the organization of research, teaching and promotion of the results of scientific work, through maintaining and cultivating a climate of openness, creativity and honesty towards oneself and toward others. It is also within the responsibility of the institution to ensure the following:

- * to make good scientific practice an integral part of the institutional corporate identity;
- * to provide an organizational framework which clearly assigns responsibility for tasks such as quality assurance in research;
- * to avoid using quantitative shortcuts (such as computing cumulative publication impact factors) when judging the quality of academic and scientific performance and achievement;
- * to have procedures in place for dealing with allegations of scientific misconduct in an expeditious and equitable way, respecting the diverging - but partially identical - interests of parties and avoiding legal pitfalls;
- * to have impartial mediators ("ombudspersons") available for those who need help in a situation of potential or actual conflict.

Independent research institutes and universities have the responsibility to develop practical rules for good scientific practice in a discussion and decision process involving all academic members they employ. It is of great importance that the procedures for managing and monitoring of established policies are formal, clear and transparent. These institutions need to have

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appropriate management structures and procedures to implement their codes of good scientific practice, including mechanisms for delegating responsibilities for direction, supervision, conflict resolution and quality assurance, taking account of each organizational unit and maintaining an effective management audit trail to verify these procedures. It is also necessary to appoint mediators to whom scientists may turn in conflict situations, including cases of suspected scientific misconduct, together with mechanisms for investigating alleged scientific misconduct. The rules of good scientific practice will affect individual scientists and it is important that they are formulated in a democratic manner, involving the entire professional staff. Once agreed upon, these rules should be widely publicized and made binding for all members of an institution, if necessary through terms and conditions of employment.

Institutional policies for good scientific practice must incorporate and reinforce any existing civil legislation or codes of practice concerning the use of animals in scientific experimentation and human patients in biomedical research. Also, several codes of good scientific practice have been built around a core of legislative requirements for health and safety in the workplace, environmental protection, data protection and individual privacy.

In the above context, mechanisms for incorporating the principles and rules of good scientific practice into the education of young scientists need to be established as well.

The guidance provided by codes of good scientific practice is equally applicable to contract research funded by governments, official agencies or commercial sponsors. As certain tensions, frequently related to the ownership and exploitation of intellectual property and to publication arrangements, can arise within research projects carried out under contract, institutions as contractors have to maintain rules to reduce or prevent circumstances that may prompt or facilitate misconduct, as well as protect their own scientists (3).

In Yugoslavia, activities related to establishment of good scientific practice and other ethical codes are at the very beginning (4,5). Thus, development and implementation of any of these codes by institutions of science in Yugoslavia, in addition to their significance for such institutions themselves, have a wider importance since they may represent:

- * an initial step in the establishment and implementation of other good practices in institutions of science as well as in other relevant institutions (laboratories, clinics, factories, etc.): good laboratory practice (GLP), good clinical practice (GCP), good manufacturing practice (GMP);

- * a factor of integrity if the recommendation for joint preparation of codes of conduct and rules of procedure is accepted by several institutes belonging to the same professional area;

- * an initial trigger for governmental institutions - ministries of science, education etc. - to approve the need for such codes through legislative.

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Good scientific practice - responsibilities of the research group head

KEYWORDS: Professional ethics; Good scientific practice; Quality assurance

The "quantum leap" science experienced during the second half of the past century has more than clearly shown the limitations of any one individual to keep abreast of both new data in one's own area of interest and the methodologies required to provide in-depth answers to any given question / hypothesis. Accordingly, science has long been recognized as a par excellence team effort. To put this in different words, since in today's science progress largely consists of small but important additions to the wealth of human knowledge rather than of large increments characteristic of the pre-industrial era, a new Leonardo da Vinci is hardly imaginable. Instead, scientific teams are made up of highly educated and motivated individuals with clearly defined tasks, coordinated generally by a senior researcher. Coordination of such different individualities by definition requires of this person - leader - head - coordinator of a research team, to strictly and even rigidly adhere to the highest ethical criteria, to allow him / her to bear full responsibility for the research carried out by the respective team. The duties and responsibilities of the head of a working group have been defined by recommendation 3 of the Recommendations of the Commission on Professional Self-Regulation in Science appointed by the Deutsche Forschungsgemeinschaft (DFG), which refers to cooperation and leadership responsibility in working groups, as "...leading a group includes the responsibility to at all times guarantee healthy conditions including communication and high quality supervision to prevent younger or more experienced group members from slipping into scientific dishonesty..." (1). Thus, the duties and responsibilities include directing research under his/her supervision as well as the actual supervision process. This encompasses coordinating the work of all team members, providing technical capabilities, as well as education of co-workers. While every scientist is personally responsible for his/her conduct, the person heading a working group is responsible for the conditions within the group as a whole. It is thus the duty of the team leader to assure that all members of his/her research team respect the principles of GSP in all stages of the research process including the finalization of a scientific work. This complex task includes the ability to provide a creative work environment, col-

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legality and internal resolution of potential conflicts within the work group as well as outside it. In case of conflict within the group, it is the responsibility of the team leader to try to resolve it exercising the least bias possible. If this proves impossible, it is his/her duty to inform senior supervisors or the ombudsman who may get involved. A significant duty of the group leader is to ensure adequate supervision of every young member of the group (grad students, young postdocs), generally by a senior member of the working group. Finally, the head of a working group is further required to warn of potential health risks of the methodologies used, if any, and to provide appropriate preventive measures. This is particularly true of work in the field of biomedicine where various, potentially harmful substances and procedures may be involved.

Naturally, the ability to fully respond to all of the above is directly related to the size of a group. Leadership demands full awareness of all relevant circumstances. In case the size of a group or engagements elsewhere (e.g. teaching) render this not feasible, the group leader needs to delegate some of his/her duties. Such a process of division of responsibilities develops naturally, for instance when a researcher other than the group head becomes the principal investigator of a project thereby personally accountable to the funding institution.

It is inherent to the scientific process that members of a working group whatever their hierarchical roles, depend on each other and thus, mutual trust is a *conditio sine qua non* of every scientific team effort. Trust, on the other hand, flourishes on the grounds of honesty, best assured by careful quality control. Healthy cooperation within a group includes independent verification of new results before they are presented to the outside world, as well as their critical interpretation. It is this process of discussion that allows new understanding and insights, and ultimately integration of new data into common knowledge, which is the ultimate goal of science as a most exciting field of human endeavor.

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Good scientific practice -training, development and mentoring of the young scientists

KEYWORDS: Good scientific practice; Mentors; Professional ethics

The conduct of science is based on internationally valid principles, the first of them being honesty toward oneself and toward others. Honesty is not only an ethical principle, but also the basis for the rules and norms of the professional conduct in science, i.e. of good scientific practice (GSP) (1). The basic principles of the scientific integrity, which must be accepted by all engaged in research and scholarship, include the highest professional standards in designing and conducting research, frankness and fairness in the scientific communication and collaboration, absolute honesty at all stages in the scientific inquiry. In this way concepts and principles of GSP provide safeguards against the scientific dishonesty and fraud. However, for full efficiency they have to be more widely adopted by universities and the research institutions and monitored for compliance.

Guidelines for GSP cover also the area of training, development and mentoring of the young scientists. According to the recommendations of the Commission on Professional Self Regulation (2), the principles of GSP should be an integral part of education of the young scientists and scholars. Universities and the research institutions should develop standards for mentorship and make them binding for the heads of the individual scientific working units.

The training and development of the young scientists is an important responsibility for all scientists, especially for heads of the research groups and the senior investigators. These activities should not be limited to providing the technical skills necessary to enable them to conduct their research. Training must also include the core ethical standards and norms of science, i.e. basic principles of GSP. Young researchers should not be invited to join a laboratory merely because the funds are available to support them, or because they provide an extra pair of hands to do the work. Furthermore, they should not generally be engaged in a project which is wholly speculative, or which simply involves the routine use of the established techniques. The project should be selected in accordance with the training and the carrier needs of the young scientists and designed so that significant results can be expect-

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ed within reasonable time. Project must be adequately supported and of sufficient duration to provide finishing of the planned research.

In the past, the young scientists have learned the principles and norms of the scientific integrity informally, by working with the senior scientists and by mentoring. Such approach was supplemented by the occasional publications that offered general advises. Currently, greater formality is needed to help the young scientists understand the importance of the scientific integrity and to adopt GSP as early as possible.

As research practice begins during the advanced undergraduate and the graduate studies, and continues by master and doctoral theses, universities should provide the formal instructions on the ethical conduct of research as part of the professional training. There is evidence that some universities now routinely provide short courses on the responsible research practice and ethic of research, i.e. principles of GSP (3). Furthermore, the publications concerning the ethical foundation of the scientific practice which are addressed to graduate and undergraduate students and the junior research workers appeared lately (1). However, besides that, fostering the scientific integrity requires initiating students into the actual scientific activity, because moral learning derives from both demonstration and practice.

The last stage of the professional education takes place during the scientific activity. Research institutions have the obligation to ensure the conditions for education promoting the principles of GSP. Universities and the research institutions need to have appropriate management structures and procedures to implement their code of GSP, including mechanism for incorporating the principles and rules of GSP into teaching curricula and the education of the young scientists. They should have in place system that allows students and the new researchers to adopt the best practice as quickly as possible.

The senior researcher and/or the research team leader must inform the young scientists about the basic principles of GSP at the start of their scientific work, and create a climate in their groups or units that encourages all to aspire the highest professional standards in the conduct of their research. As the working group usually consists of older experienced and younger, less experienced scientists, the research team leader has the responsibility of ensuring that every younger member of the group - graduate students in particular, but also advanced undergraduate, receives adequate supervision. Each one must have a senior partner primarily responsible for his/her progress. The experience of the University of Chicago with its educational "Scientific integrity" program (4) addressed to the research trainees arose the role of mentoring in educating the research ethics and the scientific integrity as the most powerful long-term influence on trainees. Mentoring is distinguished from teaching by including activities of nurturing young scientists and role modeling, in addition to the responsibility to guide the trainee in selecting and completing a worthwhile research project (5).

The research team leader or mentor has the responsibility to enable permanent and continuous consultations with young researchers and to ensure them the support of the research team. The research practice of the young scientists within the entire research program must be defined. Mentor must ensure appropriate direction of research and supervision of the young scientists including temporary check and cross check of raw data, not just computer printouts. It is important that a number of the young researchers, supervised by one senior scientist or mentor, must be limited to ensure that each trainee receives adequate individual attention. The knowledge reached through the discussion with the senior researcher or mentor is thought to be of invaluable importance for the young scientists. Because of that the choice of mentor is of great importance for them, certainly, if they are in the position to make the right one. Mentor should be a scientist with a considerable scientific productivity; otherwise, he will not be able to convey the publishing skills to the beginner.

As to the issue of mentorship, it is advised (2) that it is good practice for graduate students, beside their primary mentor, to be supervised by two additional experienced scientists, one of whom should be chosen by the student. They would be available for advice and help; they discuss the progress of the

young researchers' work with them at annual intervals. They should be accessible locally, but should not all belong to the same working group or to the same faculty or institution. Such arrangement would enable mediating in any conflict situation related to the scientific practice or other matters that might arise.

The young researchers engaged in the research program are themselves obliged to participate in all activities related to the program realization, and have the responsibility to regularly inform the research team leader and/or mentor about their research practice.

In our scientific community, the institutional code "Good scientific practice - the ethical codex of the scientific practice" is done by Institute for Oncology and Radiology of Serbia and Institute for Medical Research in January 2001, a part of it being related to the care of the young researchers. In addition, these two institutions organized two courses for young researchers about principles of GSP in the last two years. There was a great interest of all participants on this matter, indicating the need for such education.

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Good Scientific Practice (GSP) in publishing process

KEYWORDS: Good Scientific Practice; Publishing; Scientific journal

In the last two decades unusually serious cases of scientific misconduct prompted wide discussion on the research ethics (1,2). Several questions arose, and among them - is there a need for new regulations to protect science against abusive research practice?

The conduct of science rests on basic principles valid in all scientific disciplines. One of these is honesty, towards oneself and towards others. It is obvious that complete prevention of dishonesty in science is not an easy task but safeguards can and must be established. Recognizing that the research community must be able to police itself, several institutions of science initiated the formulation of rules of good scientific practice (GSP) (3). It is necessary that both institutions of science (universities, research institutes, learned societies, scientific journals, funding organizations) and every individual scientist develop a consciousness of good scientific practice and apply it in their daily practice. Serious cases of scientific misconduct in USA and several European countries prompted the appointment of the international Commission on Professional Self-Regulation in Science. Recently, the Commission published Proposals for Safeguarding Good Scientific Practice based on institutional regulations in the countries that experienced severe cases of scientific misconduct (3). The rules of good scientific practice are a core of these recommendations. As scientific activities in many fields have already been governed by legal and professional norms, and by codes of conduct like the Declaration of Helsinki. These "recommendations provide a framework for the deliberations and measures which each institution will have to conduct according to its constitution and its mission". The recommendations are principally addressed to the institutions of science, including scientific journals (Recommendation 12): "Scientific journals shall make it clear in their guidelines for authors that they are committed to best international practice with regard to the originality of submitted papers and the criteria for authorship. Reviewers of submitted manuscript shall be bound to respect confidentiality and to disclose conflicts of interest". This recommendation covers the most important issues concerning publishing - originality of submitted papers, authorship, reviewers' obligations (e.g. confidentiality and disclose conflicts of interest). Commentary relating this recommendation includes various questions of quality assurance. Several journal editors (e.g. *Annals of Oncology*) have already been following these recommendations, putting a separate paragraph on ethics in their Instructions for Authors. The

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Archive of Oncology started with this practice beginning with the volume 9. Since the very first issues of the Archive of Oncology, its editors included in the Instructions for Authors some important items already cited in the recommendations. Manuscript must be accompanied by a covering letter, signed by all authors, containing the following statements: that the manuscript has been read and approved by all authors; that the content of a submitted manuscript has not previously been published or submitted for publication elsewhere; that clinical researches have been performed in accordance with the Ethical Committee or with Declaration of Helsinki; that are no financial or other relationships that might lead to a conflict of interest. Instructions also include: demand for preparation of manuscripts according to unique rules, so-called Vancouver rules, published by the International Committee of Medical Journal Editors; demand for acknowledgment of technical help, and financial and material support; statements that authors will be notified of acceptance, rejection or need for revision within 6 weeks of submission; statement that all submitted manuscripts will be reviewed by at least two reviewers; statement that proofs will be sent to the corresponding author and demand to return corrected proof to the publisher within three days. Editorial board keeps improving the editorial policy by the addition of several points starting from the volume 9 of the journal. These are: publishing the introductory statement that the journal strictly adheres to the principles of Good scientific practice; putting a separate paragraph on ethics; preparing guidelines for reviewers of manuscripts in a form of Questionnaire that presents an official ISO document as well. A letter for reviewers that follows Questionnaire commits them to strict confidentiality and to disclose any conflict of interests, and also oblige them to review the manuscript within short time limits (two weeks are suggested); appointing an ombudsman to deal with editorial maladministration.

This last point, appointment of ombudsman, classifies the Archive of Oncology and its editorial board into those who supported the ideas of Committee on Publication Ethics (COPE) - new organization in Europe which is searching for ways to deal with publication misconduct. The COPE was set up by the editors of nine prominent medical journals (6). Although the Committee can work across the whole spectrum of publishing misconduct it is suggested that an independent body to investigate claims should be appointed. This new institution within scientific community is the institution of Ombudsman - an impartial, qualified, independent person who can advise the authors on questions of good scientific practice (3). Both Institute of Oncology (Institute of Oncology Sremska Kamenica, Good Scientific Practice-Ethical Codex of Science, 2001) and the Archive of Oncology, have already adopted this practice (4,5). Internet on-line i.e. electronic version, of the Archive of Oncology has been existing for two years. Electronic submission of manuscripts and relating correspondence through web site, <http://www.onk.ns.ac.yu/Archive/Home.asp>, is the next phase of the electronic version of the journal and should also be covered by GSP rules for publishing of scientific journals. Following the principal recommendations of the International Commission on Professional Self-Regulation in Science and the rules of the Good Scientific Practice both authors and the editors of the Archive of Oncology will significantly improve the ethical milieu of the publishing process and thus the violation of the publication ethics will be avoided or at least diminished.

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Criteria for evaluating science and scientists

KEYWORDS: Good scientific practice; Authorship; Ethics

Scientific publication is the basis for evaluating science as well as the scientists - authors of publications. Since scientific publications play the key role in the professional advancement of the scientist, the criteria for authorship or co-authorship must be clearly defined (Vancouver rules).

Through a publication authors make a new finding known and identify themselves with it. Publications intended to report new scientific findings must describe the findings completely and understandably, as well as give correct and complete references to previous work by the authors and by others (citations) (1).

Scientific journals should demand in their instructions for authors "that they are committed to best international practice with regard to the originality of submitted papers and the criteria for authorship" (Recommendation 12) (1).

It is common practice by respected journals to demand written statement, signed by all authors, that the content of a manuscript has not previously been published or submitted for publication elsewhere. Exceptions are granted only for results presented at scientific meetings.

Fragmentation, duplication or repeated publication of the same findings has led to abuses (so-called salami publication). GSP sanctions this practice as intellectual dishonesty.

The authorship of publication is derived exclusively from a creative contribution to the work (2). In the case of multiauthored papers, each author should have made a significant contribution to the conception of studies, to the generation, analysis and interpretation of the data, and/or to the preparation of the manuscript. Some journals demand this to be documented through the signatures of all authors. A so-called "honorary authorship" is inadmissible (3).

Evaluation of science and individual scientist performance is based on both quantitative and qualitative criteria.

"Universities and research institutes shall always give originality and quality precedence before quantity in their criteria for performance evaluation" (Recommendation 6) (1).

Quantitative criteria are related to productivity of the scientists, and measure the number of products i.e. publications per length of time (publication count). In many cases, the publication count is the primary factor for profes-

sional advancement (4). The current system of evaluating the scientists favors the simple counting of the author's papers; therefore, quantity outweighs quality (4). However, quantitative parameters are not sufficient for evaluating a scientist. Such practice generates the "publish or perish syndrome", thus corrupting the science by the need to produce (5). Since multiauthorship is now the norm (6,7), it has been suggested that the first authorship of scientific papers is the most suitable quantitative measure of research productivity (8). The greatest ethical problem in the gray zone between scientific misconduct and good scientific behavior refers to the definition of the true authorship (9). False, either "granted" or "ghost" authorship, is highly unethical: it destroys the mutual confidence of scientists, without which successful scientific work is impossible (1). It is worth mentioning that a great deal of work of an institutional ombudsman is related to the authorship-related complaints of, usually younger, scientists (10).

Since publication count yields little useful information unless refined by quality measures, the evaluation must be completed by additional criteria like the reputation of the journals in which the publications appeared, quantified as their "impact factors" (1). However, neither counting publications nor computing their cumulative impact factors are adequate forms of performance evaluation by themselves. The most important features that constitute the quality element of scientific achievement are the originality, "level of innovation", and contribution to the advancement of knowledge. Even in fields where intensive competition requires rapid publication of findings, quality of work and of publications (peer review) must be the primary consideration. Wherever achievement has to be evaluated, the evaluators must be encouraged to make explicit judgements of quality before anything else. They should receive the smallest reasonable number of publications, selected by their authors as the best examples of their work, according to the criteria by which they are to be evaluated.

In conclusion, it is agreed that current practice in judging academic achievement at all levels needs revision, in order to allow qualitative criteria to prevail over the quantitative ones. This approach is the essential core of the peer review system that has no alternative (1).

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Good scientific practice - Ombudsman

KEYWORDS: Good scientific practice; Authorship; Ethics

The distinction between "honest" and "dishonest" is much easier in theory, than in the actual circumstances of an individual case, with the involvement's and value conflicts which come into play.

The institution of Ombudsman has its origins in Sweden, where it was established in 1809. The word "ombudsman" is a Swedish word, which according to one scholar, refers to "a person who has an ear to the people". The definition of "ombudsman" according to the Webster's New World's Dictionary is "An appointed public official who investigates activities of government agencies that may infringe on the rights of individuals".

Ombudsmen are appointed at different levels - institutional, local, national, international, etc.

In the European Union, the European Parliament appoints the European Ombudsman chosen among persons who, besides being Union citizens, offer every requisite guarantee of independence and competence. Any citizen of the Union or any natural or legal person residing or having his registered office in a member state of the Union may, directly or through a member of the European Parliament, refer a complaint to the ombudsman in respect of an instance of maladministration in the activities of community institutions or bodies, with the exception of the Court of Justice and the Court of First Instance acting in their judicial role. The ombudsman shall inform the institution or body concerned as soon as a complaint is referred to him.

National ombudsmen are appointed in the above-described sense, as well as in different areas of life including science.

Institutional ombudsmen are those to whom their members may turn in conflict situations. In independent research institutes and universities the ombudsman is appointed by a scientific committee and is responsible on questions of good scientific practice, including cases of suspected scientific misconduct. The regulations and general conditions governing the performance of the ombudsman's duties are integral part of good scientific practice rules, prepared by institution itself.

Generally speaking, the ombudsman is impartial, qualified person, and independent mediator who investigates complaints, reports findings, and helps to achieve equitable settlements. Through its personal authority, integrity and impartiality, he/she should become a competent and credible partner to whom scientists and scholars may turn their problems and who, if need be, may take up indications for serious concern and bring them to attention of the

institution involved (1).

In independent research institutes and universities the ombudsman shall, on his own initiative or following a complaint, conduct all the inquiries which he/she considers justified to clarify in questions of good scientific practice (GSP) and its impairment through scientific dishonesty (2,3).

The ombudsman shall inform the institution or body concerned of such action, which may submit any useful comment, he must have access to all the elements required for the performance of his duties. The institutional authorities and bodies are obliged to provide the ombudsman with any information, and enable access to necessary documents, unless there are duly substantiated grounds for secrecy, and without prejudice to the ombudsman's obligation not to divulge such information and documents. All members of the institution must testify at the request of the ombudsman.

The ombudsman and his staff (usually, small committee or commission are requested) are obliged to treat in confidence any information which they have acquired in the course of their duties. The ombudsman is, however, obliged to inform the competent authorities of facts which he considers might relate to criminal law and which have come to his attention in the course of his inquiries.

The ombudsman is obliged to give annual report to the scientific committee at the end of each year.

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Good Clinical Practice - Important Aspects

KEYWORDS: Clinical trials; Informed consent; Ethics

Medical studies are either experimental (the investigator has direct control over the study conditions) or observational (the investigator has no control over the study conditions and simply observes the outcomes). A clinical trial is one of the most important examples of experimental studies. Clinical trials represent an indispensable tool for testing, in a rigorous scientific manner, the efficacy of new (cancer) therapies.

Hill defines a clinical trial as "a carefully and ethically designed experiment with the aim of answering some precisely framed question" (1). Pocock writes "The essence of a good clinical trial is that it provides truthful and precise information which is relevant to the treatment of future patients" (2).

The history of clinical trials dates to the 18th century. Several comparative trials were reported in the 18th and 19th centuries, and Rose and Armitage (1982) even describe a trial conducted in 1662 (3). The principle of randomization, introduced by R.A. Fisher in agricultural research in 1926, was first applied to human subjects in 1931. Researchers assigned tuberculosis patients to carefully matched control and treatment groups by tossing a coin, randomizing 12 patients into each group (4). This trial also introduced the concept of blinding, or masking. Patients were not told whether the intravenous injections they received were of sanocrysin or distilled water.

Good Clinical Practice. Good clinical practice (GCP) is an international ethical and scientific quality standard for clinical trials, concerning the design, conduct, performance, monitoring, auditing, recording, analysis and reporting. This is an assurance to the public that the rights, safety and well being of trial subjects are protected, and that clinical trial data is credible. The above definitions are consistent with the principles that have their origin in the declaration of Helsinki. The objectives of GCP are to protect the rights of trial subjects, to enhance credibility of data and to improve the quality of science. Clinical trials should be designed, conducted and analyzed according sound scientific principles to achieve their objectives. Scientific approach in design and analysis is essential. The essence of rational drug development is to ask important questions and answer them with appropriate studies. Scientific quality is an ethical obligation of clinical research. Clinical studies are aimed at improving the quality of management of the patients and, ideally, the treatment results of a certain disease. Principles important to follow when conducting clinical trial must be kept in mind: clinical trial is an experiment and therapeutic benefit for

the patient is not certain, any source of bias should be avoided and allocation of treatment randomized. The most important aspects of GCP are presented in Table 1.

Table 1. Important aspects of GSP

1. Ethics Committee review
2. Informed Consent
3. Sponsor responsibilities
4. Investigator responsibilities

Why we need GCP? From a young woman with metastatic melanoma, the investigators excised one of the melanoma lesions and transplanted it into the patient's mother. Subsequently, serum was withdrawn from the mother and given to the patient in hopes of producing an immune-mediated tumor response. The patient died quickly of widespread melanoma, but even more horrify, the mother died of melanoma one year later. Thalidomide experience and Tuskegee Syphilis Study put medical research process into the public spotlight (5). Not to mention German prisoner - research trials testing "time-to-death" in response to cold, heat, chemicals in healthy "volunteers".

Ethical considerations. Clinical trials are experiments on human beings and affect their health and safety. Consequently, researchers must consider several important ethical issues. Although the community may benefit from the results of a trial, no individual should be exposed to unreasonable risk. Hill proposes the following questions to be asked to ensure the ethics in clinical trial (1):

- * Is the proposed treatment safe or unlikely to do any harm to the subject?
- * Can a new treatment ethically be withheld from any patient in the physician's care for the sake of a controlled clinical trial?
- * What patients may be brought into a controlled trial and allocated randomly to any of the different treatments?
- * Is it ethical to use a placebo or dummy treatment?
- * Is it necessary to obtain a subject's consent for his or her inclusion in a controlled trial?
- * Is it proper for investigators to know which treatment is being administered to their patients?

Codes of medical ethics often stress the personal responsibility of physicians/investigators to their patients. At its 18th Medical Assembly, held in Helsinki, Finland, in June 1964, the World Medical Association produced a document (known as the Declaration of Helsinki) prefaced with a binding statement for physicians: "The health of my patient will be my first consideration".

Some general guidelines for the ethical conduct of clinical trials are:

- * The choice to participate in the trial should be that of a rational and informed person.
- * Subjects should be reasonably well informed, although they need not understand all the scientific principles that the investigator does.
- * Subjects must have the option to decline to participate, so investigators should not pressure them. Such pressure can be minimized but is difficult to eliminate.
- * The subject's interests are paramount for example, in the case of removal from the trial.
- * Certain categories of subjects are considered vulnerable - prisoners, infants and children, patients with complicated conditions, and mentally disabled persons, for example - and require special consideration when determining whether they can give their voluntary informed consent.

The basic principle of ethical medical research is that "every human subject has the right to understand the nature, and the risks and benefits of the research, and to agree or not agree to participate" (Declaration of Helsinki). This applies to every person, in every country, because it is an "inherent right" - a natural part of every person - it cannot be granted, or taken away.

Equipose. Although randomized trials are complex, expensive, and time-consuming experiments and pose some difficult practical problems and ethi-

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cal issues, they offer the most definitive method of determining the causal efficacy of therapeutic procedure.

Randomized clinical trials demand that the treatment being studied is determined by chance. And if a trial has the desired outcome, and proves one option more effective or less toxic, then some patients (typically half) will have suboptimal treatment. Physicians have professional and moral duty to treat other persons, as they would like to be treated. Should we, then, reject the conventional view of the randomized trial as the gold standard in clinical research? The answer depends largely on the interpretation of two key criteria, equipoise and informed consent, that must be met in an ethical trial. Equipoise is a balance of evidence resulting in uncertainty about which treatment is truly best. Informed consent means that patients understand what they are getting into when they enroll in a trial, and what their alternatives are.

As originally conceived, equipoise implies that doctors can put their patients on a trial in good conscience only if they believe that each treatment is equally likely to prove superior. If they think one treatment is probably better, they should give that treatment in accordance with their professional obligation. But in practice, true equipoise is elusive at best, at least at the individual-physician level. However, randomized trial is unlikely to be done if those mounting the trial do not have some reason to believe the new treatment has an advantage.

In 1987, Benjamin Freedman, Ph.D., an ethicist at McGill University in Montreal, introduced the notion of clinical or community equipoise, which widely influenced thinking about the ethics of clinical research. If there is "no consensus within the expert clinical community about the comparative merits of the alternatives to be tested," a trial can be considered ethical.

Physicians who hold opinions favoring one alternative can justifiably participate, recognizing that other equally competent and experienced clinicians hold opposite views, and that a trial may show these different views to be right (7). Many ethicists and clinical researchers accept this argument, and are comfortable with a trial as long as it addresses an issue that has not been resolved to the general satisfaction of the medical community. Instead of individual physician, appropriate medical community as a whole may determine equipoise. As long as equipoise truly exists, according to medical community, individual physician is justified to include the patient in the study, even if he is thinking different (9). However, the decision to participate in a randomized trial is not the physician's but the patient's. Thus, the informed consent is of utmost importance.

Informed Consent. The concept of informed consent acknowledges the rights of patients to participate voluntarily in clinical trial (9). This is a process of communication between a patient-subject and a clinician-investigator regarding an investigational or experimental treatment. Within this communication process, several elements must be disclosed. These include the type of research to be performed, the risks and benefits of the treatments, the unproved nature of the research, the alternatives other than participation in the clinical trial, and, finally, the subject's freedom to withdraw or not to participate in the research without any detrimental effect on the patient's continued access to adequate health care.

Verbal and written information must be supplied to patient. Consent form has to be signed and dated by the principal patient and the investigator obtaining the consent, before any trial-specific assessments are performed. Consent must be documented in patient records, i.e. patient has given consent to participate in a clinical trial (including study number and name of sponsor). Copy of patient information/consent form should be given to the patient to keep. Original signed consent forms must be retained by the investigator for inspection by the sponsor/monitor. Patient may withdraw from trial at any time, for any reason and without prejudice to their subsequent treatment and care. By signing the consent form patient authorizes the sponsor/competent authorities to examine in strict confidence, their personal medical records. Patient agrees to co-operate with investigator's requests, in respect of protocol compliance. It is assumed that patient information and consent forms are translated into the local language.

Despite a much longer history, true informed consent as defined within the clinical trial is clearly, and almost exclusively, a concept of the second half of the 20th century. A meaningful informed consent process will remain an enormously important and undeniable ethical obligation to patients who are asked to become the subjects of research. Ethics Committees should actually become an educational resource for matters related to the informed consent process and research ethics in general (10).

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Duties and responsibilities of the principal investigator

KEYWORDS: Clinical trial; Principal investigator; Ethics

The aim of this paper is to present duties and responsibilities of the principal investigator in a clinical trial.

Who could become an investigator?

An investigator could become each person who is qualified by education, training and experience to assume the responsibility for the proper conduct of the trial and who meet all the criteria required by the applicable regulations (1). Investigator also has to provide the evidence of such qualifications through curriculum vitae and/or other relevant documentation requested by the sponsor, ethical committee or regulatory authorities.

What are the duties of the principal investigator (PI)?

The principal investigator is obliged to conduct the trial in compliance with the protocol that has earlier been agreed to by the sponsor and the regulatory authorities and that has been given the favorable opinion by institutional review board (IRB) or independent ethical committee (IEC) (1,2). The investigator and/or the institution and the sponsor should sign protocol and/or an alternative contract to confirm agreement. Principal investigator should not deviate from the protocol without the sponsor's agreement and approval of the IRB/IEC.

The principal investigator has to be familiar with study drugs which means to read the investigator brochure (the compilation of the clinical and nonclinical data on the investigational product which is relevant to the study of the investigational product in human subjects) (1). It includes chemical and pharmaceutical data, preclinical and up-to-date results of clinical trials including details about efficacy and safety and action in the event of overdose.

Before starting a trial the PI has to submit all required documents to the IRB/IEC for obtaining the approval (favorable opinion) (1,2). There is a list of all documents necessary for submitting to the IRB/IEC before initiation of a clinical study. After reviewing these documents the IRB/IEC gives a letter confirming its approval or reasons for disapproval with appropriate details about the date of meeting and a list of members that attended the meeting. During conduction of trial the principal investigator communicate with IRB/IEC whenever it is necessary, e. g. to review new protocol amendments, and most importantly when reporting serious adverse events (SAE) if they occur.

The PI should anticipate the accrual rate of trial subjects, e. g. the potential number of patients intended to be included into the trial within the agreed recruitment period. He should also check the eligibility criteria for each patient

before study recruitment (1,2).

Informed consent is one of essential documents required for inclusion of the trial subject, based upon ethical principles written in the Declaration of Helsinki (3). It is written in the subjects' native language and it has to be previously approved by IRB/IEC. The investigator always gives an information that concerns patient's illness and prognosis, study drug efficacy and toxicity and details about conducting clinical study (especially diagnostic procedures and their timing required by the protocol). The investigator should explain to the patient the purpose of the trial and that the trial involves research, the study therapy and the probability of random assignment to each treatment arm (1,2). The approximate number of involved subjects, the expected duration of the subject's participation in the trial and the potential condition under which the trial might be terminated is required. He also has to inform the patient about the potential benefits and the risks if he/she enters the study, and to stress the possibility to withdraw previously given consent without any consequences to his/her further treatment.

Besides verbal communication between investigator and patient, the written patient's information has to be given to the patient. At the end of the procedure for obtaining informed consent both the investigator and the patient sign and date the written informed consent form in order to confirm, on one hand, that the investigator is responsible for conducting the trial properly and the safety of patients, and on the other, that the patients fully understand the risk and benefits of the trial therapy and accept the conditions quoted in the written information for the patient. Nobody of trial staff should force or in any way influence patient's decision of participating in the study.

The PI performs baseline and follow-up visits and is responsible for the medical decisions concerning the treatment of study participants. He may delegate some trial duties to the members of the trial staff. However, he is the only responsible person for data accuracy, e. g. base line and follow-up visits, and other trial-related assessments. So, delegation is acceptable, but abdication of responsibility is not (1,2).

The documentation concerning the study drug (its delivery, use by each study subject and return to the sponsor) should be retained at the trial site (1,2). These records include dates, quantities, batch/serial numbers, expiration dates and the unique code numbers assigned to the investigational products and the trial subjects. The investigational drugs should be stored as specified by the sponsor. PI is responsible for the correct use of the study drugs by study subjects according to the study protocol.

The investigator should have adequate number of qualified staff, and has an obligation to inform them permanently about the progress of the trial, and about any relevant data concerning trial procedures or the efficacy and toxicity of the study drugs.

The PI is responsible for the accuracy, completeness, legibility and timeliness of the data reported in the case record forms (CRF) and other required reports (1,2). All data recorded in CRFs derived from source documents have to be consistent with the source documents. Any discrepancy has to be explained. If the mistake was taken there is a strict procedure for its correction that has to be followed.

Besides to the IRB/IEC, each serious adverse event (SAE) should be promptly reported to the sponsor followed by the details about the circumstances under which event occurs, its possible relation with the study drug and its outcome (1,2). Each adverse event (AE) should be recorded as well. If the trial is prematurely closed for any reason the investigator should promptly inform the trial subjects, assure appropriate therapy and regularly perform the follow-up visits. Investigator is obliged to inform the IRB/IEC and regulatory authorities if required.

The essential documents should be kept for a minimum of two years after the last approval of a marketing application or more longer (up to 15 years) according to the local regulatory requirements or by an agreement with the sponsor. In general, PI is the sole keeper of the subject enrollment log, consents forms and source data and is responsible for prevention of their accidental damage.

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If you want to become a principal investigator, you should be sure to have enough time for (2):

* Identification of the suitable subjects - this usually involved screening the patients' hospital files;

* The contact with sponsor and the trial monitor - study sponsor undertakes a formal assessments of the study site to ensure the investigational team qualifications, and trial monitor visits the site every 4-8 weeks to check the study progress;

* Attending investigator's meetings - in some trials the sponsor asks all investigators to attend a general meeting to assure that investigators are fully informed about the trial requirements and changes;

* Trial subjects - the first visit of the subjects usually takes not less than 30-45 minutes to check the eligibility criteria, obtain the informed consent and do the baseline assessments. Moreover, plenty of time is needed for the further follow-up check-ups;

* Audits and inspections - sponsor's auditor is a person independent of routine monitoring whose task is to check for the compliance with the protocol, GCP and applicable regulatory requirements.

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Basic ethical issues in the conduct of clinical trials

KEYWORDS: Clinical trials; Professional ethics; Helsinki Declaration

Clinical trials are, nowadays, the most widely accepted tools in the search for more effective prophylactic, diagnostic and therapeutic procedures in oncology. A clinical trial is defined as an experiment on humans, being carried out in order to answer a precisely defined scientific question(s) (1). Every clinical trial must be designed and conducted in accordance with the principles of research ethics that promote respect for human participants and protect their rights and welfare.

Fundamental ethical principles (2)

Three fundamental ethical principles underlying research involving human participants are: respect for persons ("respect a person's wishes"), beneficence ("do the most positive good") and justice ("be fair").

In the field of clinical trials, these fundamental ethical principles find expression in the requirement for:

- a) Informed consent of prospective participants ("respect for person"),
- b) Risk/benefit assessment and balance before and during the trial ("beneficence"), and
- c) Fair selection of individual research participants with the protection of vulnerable communities/groups ("justice").

The informed consent

Research participants should be treated as autonomous beings, capable of making an informed decision whether to participate in a research. A consent should be requested after the participant has been adequately informed about the research, has understood the information and the right to refuse to participate or to withdraw from the research at any time without harm. The process of obtaining informed consent is thus, based on three elements: information, comprehension and voluntariness. Preferably, the consent should be given in writing. If a participant is not capable or is legally incompetent of giving informed consent it must be obtained from a legally authorized representative.

The risk/benefit assessment

The Hippocratic maxim "do no harm" applied to the field of clinical trials means that one should not injure one person regardless of the benefits that might come to others (science and society). The principle of "beneficence" obligates the investigator to maximize benefits and minimize harm that that

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might occur from the research. Every clinical trial must be preceded by sufficient preliminary testing (laboratory, animal or human experiments) and the researcher must decide when it is justifiable to perform a research seeking for certain benefits despite the involved risks and burdens. Balance of risks and benefits should also be monitored and preserved during the trial.

The distributive justice

Individual subjects or communities should be selected for participation in such a way that the risks of the research are equally distributed and benefits will be equally enjoyed. The investigator should be aware of the ethical problems of research involving vulnerable subjects (relatively or absolutely incapable of protecting their own interests, for example: children, patients with diminished capacity to consent or terminally ill) or communities (i.e. developing countries), justify the involvement of these subjects and include additional safeguards for their safety and welfare.

International research ethics guidelines

The Declaration of Helsinki (DoH) is the most widely accepted code of research ethics (3). Historically, the DoH stems from the Nuremberg code (4), which was written as a reaction to the horror of the Nazi experiments on the concentration camp prisoners during the Second World War. The full title of the Declaration is "Ethical Principles for Medical Research Involving Human Subjects". It was adopted by the World Medical Association General Assembly in Helsinki (1964) as a statement of principles to guide physicians and others engaged in medical research to protect human participants and conduct their research in an ethical manner. It must be fully known and followed by the research team. The clinical trial protocol should always contain a statement of the ethical considerations involved and should indicate that it is compliant with the principles of the DoH. Other research ethics guidelines that are adopted by most nations are the CIOMS International ethical guidelines for biomedical research involving human subjects (1993) (5) and ICH Guideline for Good Clinical Practice (ICH-GCP, 1997) (6).

Responsibilities of the investigator (3, 5, 6)

The investigator and the research team have a fundamental responsibility to safeguard "the life, health, privacy, and dignity" (5) of the people participating in their research projects

by assuring that:

- * the research question is carefully defined;
- * the study is properly designed, scientifically sound to permit valid conclusions and formulated in an experimental protocol;
- * the study is approved by an independent ethical committee (see below) and conducted according to the protocol;
- * the participants meet eligibility criteria;
- * the informed consent is appropriately obtained, free of coercion or undue influence;
- * risk /benefit balance is monitored and preserved during the trial;
- * all changes of the protocol and adverse events are reported to the Ethics Committee and regulatory authorities;
- * all members of the research team are medically qualified, trained in research methods and methods of human research participants protection.
- * privacy of the research participants and confidentiality of research data is protected

The role of ethics committee (3, 5, 6, 7)

Together with the investigator's responsibility to protect human subjects in a clinical trial and the requirement for informed consent of prospective participants, an additional assurance that subjects are protected is provided by an independent ethical committee (EC).

The EC is responsible for reviewing:

- * the scientific justification for proposed research and the use of human subjects

- * the justification of predictable risks weighed against the anticipated benefits for the subjects and others
- * the standard of care ethically required for participants in a proposed research
- * the adequacy and completeness of information for potential participants and informed consent process/forms
- * the procedures for recruitment of research participants
- * the qualifications of the investigator, research team and suitability of research site
- * the information about payments and compensation available to participants

Before initiation, every clinical trial must be approved by the EC. The EC should also monitor the ethics of ongoing trials. The investigator has the obligation to communicate with the EC and to submit all documents and information necessary for the review.

In conclusion, the duty of the physician is to safeguard but also to promote the health of people through clinical investigation. Research ethics guidelines are needed to provide a necessary framework for responsible codex of ethical human research.

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