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Journal

Acta BioMedica, 91(Suppl 13)

ISSN

0392-4203

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Publication Date

2020

DOI

10.23750/abm.v91i13-s.10643

Peer reviewed

Acta Biomed 2020; Vol. 91, Supplement 13: e2020016 DOI: 10.23750/abm.v91i13-S.10643

Review

Ethics committees for clinical experimentation at international level with a focus on Italy

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Abstract. Guiding legislation and associated bureaucracy for the ethical review of clinical trials observational studies and food related research play an important role in the competitiveness of a nation in the face of tough global competition to attract sponsors and investigators. This is of particular relevance in the case of multicentre trials and multidisciplinary research. Accordingly, in this report we tried to gather in-depth knowledge of the current role and practices of ethics committees nationwide in both clinical and research settings. This mini-review aims to describe the formulation and organization of ethical committees in Italy in order to provide a focus for deliberations on ethical issues in medical and scientific research in line with human rights, as set out in the European Union charter. Furthermore, we evaluated the impact of an institution's ethical committee intervention on reducing the time required to obtain an opinion from Research Ethics Committees by guiding investigators in addressing ethical issues in their proposed studies. (www.actabiomedica.it)

Key words: Ethics Committee, Italy, Clinical trials, Observational study, Food related research, risks, ethics

Introduction

Bioethics is a discipline dealing with ethical issues in biomedical and biological research. With the ongoing advance of science and technology, the concerns related to safety and security of human subjects have increased tremendously. This requires that biomedical research and health care activities, as well as proposed scientific activities, must be reviewed by independent authorities according to national, supranational and international legislation. This required the establishment of ethical committees (ECs) to ensure that research and health care practices are carried out in an ethically acceptable manner.

Ethics Committees (ECs) are independent, multidisciplinary, non-profit bodies. They are constituted to evaluate clinical experimentation and research involving human subjects and routine patient care from an ethical and scientific point of view, in order to ensure that these abide by the ethical standards set by national and international guidelines (1). These committees are deployed to analyse the ethical concerns related to patient care or research involving human subjects (2). Depending upon their specific roles, the ethical committees are of two types: Research Ethics Committees (RECs), and Clinical Ethics Committees (CECs) (3,4). RECs deal with the evaluation of research projects and protocols so as to protect the rights, safety and wellbeing of human subjects involved in clinical research and trials, while CECs are responsible for addressing the ethical issues related to daily clinical practice, bioethics training, and the development of ethical guidelines (3,4).

History and importance of Ethical Committees

The establishment of ethical committees has been a relatively short journey. In the early second half of the 20th century, review bodies started to emerge, mainly as a form of self-regulation within the medical profession, and often in an ad-hoc form in response to specific problems. However, in past decades Research Ethics Committees (RECs) have been established in most European countries and worldwide as permanent and independent bodies (4,5). As such they form, at least in Europe and other western countries, the core of a robust infrastructure which monitors and reviews research projects. Several supporting initiatives have been also promoted e.g. by the World Health Organization, in establishing the Global Network of WHO Collaborating Centres for Bioethics (https://www.who.int/ethics/partnerships/global_network/en/).

The history of the formation of ethics committees dates back to the 1960s, when the US National Institutes of Health established a policy regarding the ethical review of all research projects submitted to the US Public Health Service for funding (5). This initial act stimulated debates which took place on ethical concerns regarding clinical studies involving human subjects. These debates resulted in the National Research Act 1974, with the subsequent establishment of the Institutional Review Board (IRB) system to oversee clinical research practices involving humans (6). Further developments led to the establishment of a National Commission for the Protection of Human Subjects of Biomedical and Behavioural Sciences, to safeguard individuals participating in clinical trials and to develop guidelines for biomedical research. The Commission mandated that all research protocols involving humans must seek approval from the IRB. At the same time, the President's Commission for the Study of Ethical Problems in Medicine and Behavioural Research was established to examine ethical issues involving health care services and professionals, which led to organization of clinical ethics committees (CECs) for addressing ethical issues of clinical practice (2,6).

Research ethics in Europe

Meanwhile in 1964 in Helsinki, Finland, the World Medical Association adopted a declaration on research ethics as a reaction to malpractices revealed during the Nuremberg trials (7). Since then, this declaration has been extensively reviewed. However, the main focus and the central ideas remain unchanged (8). The declaration sets out ethical principles for biomedical practices and research involving human subjects, the basic principle being the prioritization of the safety and well-being of human subjects, followed by principles for medical research and, additionally, for

medical research combined with medical care (8). The EU regulatory framework emphasizes the explicit EU commitment to human rights, illustrated by the Oviedo Convention (9) which was adopted by the Council of Europe in 1997, and also by the European Charter of Fundamental Rights (10). This convention addresses the ethical issues raised in research within the framework of human rights protection (9). It sets out principles to ensure the welfare of human beings, and to ensure informed consent and privacy (9).

Ethics is given the highest priority in EU funded research: all the activities carried out under Horizon 2020 must comply with ethical principles and relevant national, EU and international legislation (see e.g. https://ec.europa.eu/programmes/horizon2020/en/h2020-section/ethics) The most common ethical issues include those relating to the involvement of children, patients, vulnerable populations, the use of human embryonic stem cells, privacy and data protection issues, research on animals and non-human primates, misuse/malevolent use, food security and safety, impact on the environment, etc. It also includes the avoidance of any breach of research integrity, which means, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct. The EU ensures that the research it funds complies with core ethical values in all phases of research. Even though research ethics are more established in medical research, it is equally pivotal for all scientific domains. For that reason, professional and academic associations formulate policies and guidelines with ethics codes, adapted to their specific research domains.

Recently, the EU has implemented its Regulation 536/2014 on clinical trials (11), aiming to increase the efficiency and rapidity of the procedures for approving trials, simplifying sponsors' obligations and guaranteeing public access to trial-related data. The regulations attribute to the ECs the freedom to organize their activities in accordance with each EU member state's legislation. *De facto*, Regulation 536/2014 has reduced the number of ECs and increased the workload in clinical trials, and the activity addressing ethical issues in every-day clinical practice is further diminished (12).

Table 1. Number of Research Ethic Committees (RECs) and accountability of RECs at different levels in EU countries (13)

Country	Number of RECs	Type of REC-Accountable to whom
UK	80+51 for non clinical trial of an investigational medicinal product.	All RECs—UK Ethics Committee Authority or the body they have nominated
Austria	26	University REC—medical faculty Hospital REC—hospital head Outside hospital—regional government
Belgium	215	Central REC—government University REC—medical faculty Outside hospital—institute where situated
Bulgaria	103	Central REC on drug trials—Ministry of Health Central REC on research ethics— Ministry of Education and Science Local REC—central REC
Cyprus	3+1 central	Central REC—Ministry of Health Local—none
Czech Republic	9 multicentre, 100 local	Central REC—none Local REC—none
Denmark	11	Central REC—none Regional REC—central REC

(continued on next page)

Table 1 ***(continued).*** Number of Research Ethic Committees (RECs) and accountability of RECs at different levels in EU countries (13)

Country	Number of RECs	Type of REC-Accountable to whom
Estonia	2	Regional RECs—none
Finland	5+1 central	Central REC—Ministry of Health Regional REC—board of the hospital district
France	40	Central REC—none Institutional REC—none Local REC—none
Germany	53	Central REC—Federal Chancellor Local REC—institution where situated
Greece	One in each region and hospital+1 central	Central REC—Ministry of Health Regional and local RECs—none
Hungary	Several regional and local+1 central	Central REC—Ministry of Health Regional REC—central REC Local REC—regional REC
Ireland	13	Local REC—Ethics Committees Supervisory Body
Italy	90	National bioethics committee—Prime Minister Central REC—Ministry of Health Local REC—none
Latvia	4 regional+1 central	Central REC—none Regional REC—central REC
Lithuania	3	Central REC—Ministry of Health Regional REC—central REC
Luxembourg	1	No information available
Malta	3 local+1 central	Central REC—university Local RECs—institution where situated
Netherlands	30 regional+1 central	Central REC—Minister of Health and Parliament Regional REC—none
Poland	52+1 central	Central REC—none Local RECs—central REC
Portugal	Several local+1 central	Central REC—Minister of Health Local REC—institution where situated
Romania	1	Central REC—Ministry of Health
Slovakia	8 regional+ about 60 local+1 central	Central REC—Minister of Health Local REC—Minister of Health
Slovenia	Several local+1 central	Central REC– none Local REC—central REC
Spain	136	Local RECs—none
Sweden	6+1 central	Central REC—none Regional RECs—none

Ethical Committees in Italy

Historical milestones

The situation of ethics committees (ECs) in Italy is at a critical point, because of a number of factors emerging from new technical and scientific advances, new legislative requirements and lack of harmonization of procedures. To look into the issue in greater depth, it is important first to understand the establishment and organization of ethical committees in Italy. The organization of ECs is quite different in Italy to the rest of the EU. The first EC was created in 1973, with the aim of ensuring that research for new medical treatments was "for a person and with a person, never on a person" (14). In the 1980s, there were few bodies in Italy that could be regarded as ECs (regionally, in public bodies or in universities). It was only on 28th March 1990 that the Italian National Bioethics committee was established, according to a decree signed by the President of the Council of Ministers (15).

The Italian National Bioethics Committee (NBC)

The NBC consists of 40 members. including a Chairman, two vice-Chairmen and experts from various medical specialties such as biology, jurisprudence, psychology and philosophy. These members are appointed for a period of three years, with membership being interdisciplinary and diverse, thus bringing together different experties on a single platform. The Committee holds monthly plenary sessions and has five sub-committees focused on specific areas, dealing with bioethical issues in the human genome and biotechnologies, artificial insemination, biomedicine, protection of critically ill subjects, moral epistemology and bioethics training. The tasks assigned to these committees are to give opinions, prepare legislative acts and address ethical and legal problems associated with the impact of scientific and technological progress on human life. The NBC also maintains relations with Ethics committees and legislative bodies at European and international levels (16).

Regulatory framework of Ethics Committees in Italy

A fundamental step for clinical regulation in Italy was the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use (16). This was achieved through Legislative Decree No 211 of 24 June 2003 (the latest version of the Helsinki Declaration, the Oviedo Convention, good clinical practice standards and the guidelines on the evaluation of the effectiveness of clinical trials updated by the European Agency for the Evaluation of Medicinal Products). According to Article 2(1)(m) of the Decree, an EC is "an independent body consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection […]" (17).

Regional and local Ethics Committees

In last two decades, regional and national ECs were established in Italy within hospitals, university polyclinics, biomedical research bodies and institutions. According to Article 1 of Legislative Decree No 211 regarding clinical trials on medicinal products, the ECs should verify the applicability of proposed trials by critically evaluating their rationale, the relevance of protocols (objectives, design, operation, result evaluation), the competence of researchers, and should assess all ethical aspects, with respect to informed consent while ensuring protection of privacy in the use of biological samples. Moreover, "The competence of each Committee may concern, in addition to clinical trials on medicinal products, any other issue they might be entrusted with according to international practices, namely the use of medicines and medical devices, surgical and clinical procedures or procedures related to studies on food products on humans" (Law 8 November 2012, No. 189, Art. 12) (18).

The organizational structure of regional ECs is represented by the Regions. Each Ethics Committee is in charge of one or more provinces, in order to comply with the standard of one Committee per million inhabitants, without prejudice to the possibility of providing an additional Ethics Committee, competent to act in one or more scientific hospitalization and care institutions (Law 8 November 2012, n. 189, Art. 5). Some of the ECs have a national mandate that identifies their expertise in a particular area. Amongst these are the Ethics Committees of the National Institute

of Health (Istituto Superiore di Sanità, ISS) and the "Celio" Military Hospital (Decision of Lazio Region of June 12, 2013) (19).

Further developments in regional and National Ethics committees in Italy

The latest EC guideline is the Ministerial Decree of February 8, 2013 (20) which specifies that ECs are independent bodies that ensure the rights, safety and wellbeing of subjects enrolled in clinical trials, and evaluate those trials on scientific, ethical and procedural bases, thus guaranteeing public protection. Moreover, this Decree allows the ECs to promote consultation on ethical matters pertaining to scientific and clinical activities in the case where these have not been assigned to any other specific bodies. Hence, the overall objective is to promote human values and to safeguard the self-esteem and value of human subjects. In addition, ECs can propose bioethics training for health professionals. Furthermore the legislation in 2014 (EU) No 536/2014 ; Article 8 ("Decision on the clinical trial") states that: "Each Member State concerned shall notify the sponsor through the EU portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused, notification shall be done by way of one single decision" (21). This resulted in a national debate on reducing the number of ECs. As a result, a gradual decline in the number of ECs in Italy from 243 in 2012 to 91 in 2014 and 90 in 2019 (22) took place. Furthermore, Law No 3 of 11 January 2018 (23) promoted a further reduction in the number of ECs. Two decrees issued by the Minister of Health following this law required the identification of a maximum of 40 local ECs and 3 national ECs, of which one would be reserved for the paediatric environment. However, implementing this reform is difficult in practical terms, as legislation for establishing local ECs and national ECs has still not been enacted. A further provision of this law was the establishment of an Italian Medicine Agency (AIFA) and a National centre for the coordination of regional ethics committees for clinical trials of medicines and medical devices for human use (23).

Following an EU regulation, the NBC suggested that CECs should be given legislative and administrative attention. A further Legislative Decree No 52 of 14 May 2019 was issued for the 'Implementation of the designated powers to review and reform the regulatory provisions in relation to clinical trials on medicinal products for human use, under Article 1(1) and (2) of Law No 3 of 11 January 2018 (23)'. Certain provisions in this Decree might have a significant impact on clinical trials. For instance, sponsors are permitted to transfer data and results from non-profit trials for registration purposes. Until now, the use of data obtained from non-profit trials for registration purposes has been restricted. The sponsor or transferee is, however, required to pay and to reimburse the direct and indirect costs incurred in the trial. Moreover, if the study is further reclassified as profit-making, they have to pay the corresponding charges, including any returns from the exploitation of intellectual property. A Decree of the Minister of Health was enacted on 31 October 2019 to stipulate measures intended to enable and support the performance of non-profit clinical trials and observational studies, as well as to identify measures for ensuring coordination between public and private sponsors for clinical trials set up for post-marketing surveillance of medicinal products. That Decree also established an order, enacted by the AIFA, to identify suitable procedures to assure the independence of clinical trials, ensuring that no conflict of interest should arise in the assessment of subsequent applications.

Ethical guidelines for observational studies

In the health sciences, observational studies are those studies in which an investigator considers the variables of interest without his actions in any way influencing the condition of the subject or subjects studied. Observational studies are different from experimental studies, in the sense that in these studies no intervention other than recording, classifying, counting and analysing of data takes place. In observational studies the investigator has no control over the study variables and merely observes outcomes. Most observational research is epidemiological or health services research, but some observational studies, include case series and case studies, are conducted by clinicians in personal care settings (24).

Observational studies can be classified into case control studies, cohort studies, cross sectional studies, case reports, case series, and descriptive studies which add generalizable knowledge about health or disability issues. These studies play an important role in ensuring the public interest in a safe environment and in safe and effective health and support services. These studies might examine the exposure of humans to chemicals in the environment or to medicines resulting in diseases and disorders. In addition, these studies are used to identify any gaps in health and support service provision, and this obliges service providers to inform consumers that studies of this type are of utmost importance in improving the quality of the health and support services. They should also give consumers details of the measures taken to protect participants from harm (24).

Ethical requirements and regulations pertaining to observational studies

Investigators conducting, or involved in conducting, observational studies are responsible for ensuring that these studies meet ethical standards. Observational studies might or might not require informed consent and rigorous EC review. When there is more than one investigator, the principal investigator has the overall responsibility for the ethics of the activity. The ethical guidelines regarding observational studies generally vary depending upon the type of study, and might not be subject to EC review at all. For that reason clear guidelines for such studies are scarce. Currently, approval by ethics committee is mandatory for all research in Canada, including the analysis of patient records (25). However, no such requirement exists for retrospective studies in, for example, Turkey (26).

Current legislative provisions in Italy pertaining to observational studies are the following:

1) The Italian Ministry of Health circular n. 6, 2002, which defines non-interventional (observational) trials (27)

2) The Italian Legislative Decree n. 211/2003 on clinical trials of medicinal products, which also gives a definition of the "non-interventional" trial (observational study) (17)

3) The 20 March 2008 ruling of the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) which gives guidelines for the classification and conduct of observational drug trials (28).

Since the publication of the first Italian legislation, as mentioned above, considerable attention has been paid to defining and approving observational studies by the clinical and epidemiological research sector. Following the publication of these regulations, a significant increase in the number of observational ("non-interventional") study protocols was submitted to ethics committees for evaluation in Italy.

However, because there is no clear legislation in this area from the EU, the ECs have difficulty in defining, interpreting and implementing existing regulations. Under EU human rights legislation, it can be inferred that observational studies should ensure respect for and protection of people participating in these studies, with a fair distribution of the benefits and burdens. The study should be designed in such a manner that inclusion and exclusion criteria for participants are fair. There should not be any discrimination on the base of age, sex, disability or religious or spiritual affiliation, except where it is essentially important to do so. Investigators should respect diversity among participants, and conduct honest and thoughtful inquiry with rigorous analysis. Conflict of interest should be avoided in the case of multidisciplinary and multi-centre research.

Just as the registration of clinical trials has an ethical and scientific rationale, registering observational studies at approved locations reduces duplication, ensures monitoring of projects with respect to ethical guidelines, provides global access to and improves the credibility of the information, and ensures transparency of research, thereby creating a knowledge bank. However, observational studies are prone to publication and reporting bias due to lack of regulations regarding registration and reporting. Hence, registration of these studies provides them with authenticity and rationale (29,30).

Presently, ClinicalTrials.gov in Canada and US (31,32) and the European Union electronic Register of Post-Authorisation Studies (EU PAS Register) in the EU are publicly available for the registration of post-authorisation studies, in order to improve the transparency of observational research (33). Over the past few years, the number of observational studies regis-

tered per year has increased, and observational studies now represent about 15% of all studies on ClinicalTrials.gov. Approximately half of these studies are from North America followed by Europe (20%) and Asia (13%), where 85% of these are funded by non-industry sources (31,34).

There is a considerable debate over the requirements of the EC committee for approval of observational studies. Some researchers are of the opinion that EC review is not required because these studies are not sensitive with respect to ethical concerns while, on the other hand, other researchers emphasise the need for EC review of each observational study. (35-38).

To harmonize the process of reporting of observational studies, in 2004, an international initiative, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), was launched. STROBE provides complete guidelines on reporting observational studies such as study design, participants, and results However, ethical requirements and registration procedures are not addressed (39).

The International Committee of Medical Journal Editors (ICMJE), along with specific international journals, however, has clearly stated that submitting publications based on observational studies requires ethical approval, or at least a letter from an EC if ethical approval is not required (40-44).

Ethics in food research

With the increasing world population and extensive urbanization, the production of enough food to feed everyone is a huge challenge, not only for agriculture research and industry but also for food and nutrition related research and industries. As this area is directly related to the wellbeing and safety of humans and involves the use of animals both for research and as a food source, there are ethical concerns which are governed by relevant guidelines and procedures (45,46). Food and nutrition research is a diverse field with many aspects that raise ethical concerns such as research and development of new products and processes (e.g. GMOs), consumer behaviour, health claims, supply chain, agricultural practices, food safety and security, sustainability, regulation, trade and emergency food aid. Ethics plays an important role in all these areas and frequently gives rise to questions and challenges concerning issues and practices in food related research. There are moral, cultural, social and spiritual values related to the personalization of food among various regions of the world, and this also results in ethical considerations when embarking on food related research (47).

Risks to humans, animals and the environment

General ethical principles in food research are the same as in other research arenas; they include personal safety and wellbeing, safeguarding the prestige and honour of participating human subjects, ensuring equal distribution of benefits, equity and justice, and informing participants about harms which might arise during experimental and non-experimental methods, including observational studies, interviews, web-based data collection (especially in the case of vulnerable groups such as children), exposure of participants to stressful and uncomfortable situations etc. In addition, while designing the study, the researchers should give thorough consideration to potential risks and to ethical issues related to society, animals and the environment, and should take necessary precautions to alleviate and avoid adverse effects.

In case of research involving animals, researchers should ensure animal welfare and the three Rs for animal research i.e. replacement, reduction and refinement, to keep their suffering to a minimum. Cell and tissue cultures should be used wherever possible, replacing animals. Endangered species or species at risk should be avoided. Biotechnological research, particularly that involving GMOs, is of particular concern with respect to threats to the environment. Research in this area should be a balance between risk and benefits (47,48).

Ethical considerations in food research methodologies and multidisciplinary research projects

Food research involves various methods. These may encompass but are not limited to research, equivalent to medical research, which involves clinical trials to check the safety of food in human subjects with

respect to allergies, nutrigenomics, and neuropsychology of food choice. Research involving medical interventions such as MRI and other technologies requires critical ethical review. Human tissue samples might be required in pharmacokinetics and pharmacodynamic studies. In addition, observational studies involving large groups of consumers require prior consent from every participating individual. This could however potentially make the research impossible. This prior consent may not be required when research is being conducted in public places such as restaurants, canteens and supermarkets. However, such researches need to address the issues related to consumer privacy, and this should be explained to both consenting and non-consenting participants. On the other hand, research carried out in private homes, small social and cultural groups and hospitals requires rigorous prior informed consent, data confidentiality and privacy protection. In the case of identifiable data such as pictures, videos and audio recordings, informed consent should be obtained in respect of release of data to third parties. Where such consent is unavailable, participants should not be subject to disclosure of identifiable data pertaining to themselves (46,47).

Studies involving covert research should only be done where collecting data by any other methods is impossible, where risks to participants are minimal, and where anonymity is guaranteed. These projects should undergo rigorous review by RECs. In addition to observational and covert studies, technological advance has paved the way for utilization of social media for data collection in food related research. This method might be of interest to people who want to avoid face-to-face interviews. However, special ethical consideration should be given to vulnerable groups like children and teenagers. Other ethical concerns in this regard arise in respect of recruitment, consent, privacy and authenticity of the data (47).

Mostly, food related research is multicentre and multidisciplinary. It is carried out in many countries, and might include working in developing countries. This requires the establishment of principles of equality and benefit to the local population, as well as the assurance of biological diversity with respect to sharing of the benefits of genetic resources as food products and/or nutraceuticals. Specifically, when research is carried out in hazardous situations, the health and safety potential risks to researchers and local participants must be identified. In addition, security and confidentiality of data must be ensured (47,48).

Ethical concerns related to nutrigenomics, functional, nano-based and genetically-modified (GM) foods

Nutrigenomics is based on the effect of nutrition on gene expression related to health. This helps to identify the response of individuals to a particular diet that allows personalization of dietary regimes in order to obtain maximum health benefits thus leading to the development of commercial functional foods. A potential conflict may arise in this regard between the requirements of genetic data and non-medical data. Therefore, all types of data collection should be under strict ethical control. Furthermore, nanotechnology, nutrigenomics and genetic engineering, deployed to develop functional consumer oriented foods that require clinical trials, may give rise to various ethical concerns such as health claim labelling (EU regulation No. 1924/ 2006) to ensure consumer satisfaction in terms of safety and choice of foods. Based on ethical concepts and arising from misconceptions regarding nano-based and GM foods, these foods must be labelled with a 'clinically tested to be safe' statement (47-49).

Specifically, proper risk assessment of nano-based foods should be conducted in terms of consideration of potential health hazards such as biotoxicity and bioaccumulation in human tissues. Therefore, checking the safety of such foods is of utmost importance. Moreover, in the case of animal involvement in a study, relevant ethical procedures should be implemented including the development of *in vitro* procedures wherever feasible.

Ethical issues in food security, sustainable food production and distribution.

Food security legislation primarily focuses on ensuring sustainable production, distribution and marketing of food, in adequate amounts to make it physically, socially and economically accessible, in order to meet the dietary requirements and food choices of all

people of the world, and thereby to reduce hunger and safeguard survival. However, despite efforts in this field, approximately 900 million people are chronically hungry and up to two billion suffer from intermittent food insecurity. It is therefore necessary to consider the ethical questions surrounding the integration of nutrition into the food security concept. Key ethical issues include, but are not limited to, making societal decisions and defining values of food security that have an impact on nutritional outcomes, and the ethical balance between environmental sustainability and meeting individual dietary and nutritional requirements. Issues related to overgrazing, extensive farming putting animals at risk, use of alternative protein resources and corresponding public acceptance issues make the situation even more cumbersome. Hence, such complex issues should be given thorough consideration to ensure global food security (46-49).

EU's new legislations and competitiveness of Italy in Clinical Research

Good clinical practice and fair clinical trials are integral components of health based research. In an effort to simplify and standardize the rules and regulations of clinical trials across the EU, the European Clinical Trials Directive 2001/20/CE (ECTD) was introduced in 2001. The ECTD stressed good clinical practice and ethical values, to ensure the safety of trial participants (17).

Despite the fact that ECTD was an evolutionary approach, it failed to achieve its aims, as each member state was permitted to follow the ECTD guidelines autonomously. That made room for contradictory decisions by competent local authorities. As a result, each member state has its own procedures for submission and processing of the proposals. It specifically affected sponsors that aimed to conduct multicentre trials in different member states, which obliged them to submit different applications in different members states, and sometimes in each centre (49,50). This considerably increased the time required for processing and approval of applications and for conducting the trials. Besides that, compulsory insurance cover for trials and higher management costs led to a tremendous increase in the overall expenses of trials, making them unaffordable for independent research organisations and not-for-profit institutes (50-52).

Consequently, the EU became less attractive for the pharmaceutical market, thus significantly reducing the number of CTs (53-55). The situation became even worse for Italy, which, despite being Europe's third largest bio-pharmaceutical market with outstanding research and leadership in the medical milieu, witnessed a marked decline in CTs. As a result of the ECTD, a lack of interest from sponsors, scarcity of public funds for clinical trials and multiplicity of Ethics Committees, there was a record decrease in CTs (56,57). For instance, Italy recorded a 21% reduction in CTs from 2008 to 2012 (58). According to EudraCT (EU clinical trial database), Italy's share of total projects registered in the US National Institute of Health's (NIH) database has decreased from 18.5% in 2008 to 17.7% in 2012, in contrast to the rest of the EU member states (59,60).

This decrease in registered multicentre trials might be in part due to the cumbersome administrative procedures required for submission of documents, review and approval of trials and signing of contracts after approval of CTs by independent ECs. For instance, a survey was conducted on 134 Italian Independent ECs, for a single trial by Porcu et al., 2008 (61). This revealed that there is a huge variation in the application procedures for CTs with respect to the number and the format of required documents, with the number of necessary documents ranging from 6 to 21, with 57% of the surveyed ECs requiring at least one personalized document. The number of hard copies required ranged from 6 to 249, while 26.9% of ECs demanded e-mail or CD-ROM submission (number of copies ranging from 1 to 15) as well as the paper version (61). This lack of harmonization in internal procedures and guidelines was further reported by another study conducted in 2009 where a survey on the practice of ethics committees in 10 European countries was conducted (62).

As per the EFGCP report (2012), this variation in "centre-specific" documentation in Italy was largely due, to the high number of Independent ECs. Italy had the highest number of national, local and regional ECs when compared to the rest of the EU member

states. The high number of IECs resulted in a confusing situation, particularly for the acceptance or refusal of an opinion. With respect to number of ECs. Italy had 260 ethics committees, the United Kingdom had 120, Germany 50 and France only 25 (63).

Italy ranked last among nine EU countries with respect to the number of NIH-registered trials per capita in a SAT-EU study conducted by Marta Gehring and co-workers in 2015. This ranking was based on surveys distributed to pharmaceutical companies, medical device manufacturers, Clinical Research Organizations and academic Clinical Trial Units (CTUs) (64,65). Italy scored low in all four of the criteria tested, i.e. ranking 10th out of 12 countries in the availability of trial-related information, 12th on the predictability and speed of ECs/ IRBs, and 9th on the availability of required equipment. It ranked 7th out of 9 on its general attractiveness as a place to conduct clinical trials. This low score assigned by highly ranked market participants with decision making power in trial investments is an alarming situation for a country with a history of scientific excellence. With respect to the setting up of multicentre trials, the participants were of the opinion that the EC's procedures and contracting processes in Italy are so painstaking and sluggish, that, by the time an international multicentre trial is under way, the Italian site could still be in process of setting up. That is the main reason that, despite a desire to include Italy in the conduct of CTs, they do not participate (66). The study concluded that the reasons for this lack of interest in CTs in Italy are the bureaucratic procedures, penalizing the high scientific level and research standards of the Italian Investigators (67). This is more apparent in the case of independent research organisations that usually takes longer to establish trials, have limited financial resources, and involve professionals who do not have the benefit of permanent employment contracts (67-70).

The SAT-EU Study Group suggested that the implementation of simplified legislation governing CTs, reduction in the number of ECs, consistency in contracts and the establishment of qualified CTUs will enhance international interest in setting up CTs, thus improving the status of clinical research in Italy (64,66). Nonetheless, the implementation of the ECTR (replacing ECTD; *Regulation (EU) N.536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use*' adopted on 16 April 2014 (11)) that aims to speed up the application process by centralizing, synchronizing and simplifying the administrative documentation for multicentre CTs across the EU, will definitely improve the situation in member states (71). The new ECTR has very ambitious goals: to push Europe to be more competitive in the CTs scenario, to improve transparency, to create a simplified regulatory system and to increase public trust (55,71).

Proper implementation of any ethical legislation depends upon the awareness of the public in general and concerned people (management staff, researchers, reviewers, participants, ECs, investors etc) in particular. For instance, if researchers are not aware of the rules and regulations regarding ethical issues pertaining to their research, they will not be able to meet the requirements set by the ECs in line with national and international standards. This will result in potential delays in obtaining opinions from the concerned ECs. The same is the case regarding the proper utilization of the benefits of ECTR.

Recently in a study, two separate surveys addressed to Clinical Research coordinators (CRCs) and Clinical Investigators (CI) were conducted by Cagnazzo et al., (2017) in an attempt to investigate the perception and knowledge of the new regulations (ECTR) by Italian professionals (72). The study highlighted that the institutional channels and the managements of Hospitals/Institutes are not taking appropriate measures to inform clinical researchers about the ECTR, and neither have they documented plans to do so; acquiring this information is still very much a personal initiative of the researchers. Moreover, they highlighted that slow bureaucracy, inadequate English language skills and low susceptibility to change accounts for Italy being not ready to accommodate changes brought by ECTR (72).

Role of internal ethics committees in expediting the approval process of a research project

Be it clinical research, an observational study, food science and nutrition or biotechnological research, the

potential harm to human subjects and to animals in particular, and to the overall environment in general has necessitated the development of certain ethical guidelines to ensure that a project is conducted according to national and international ethical standards. However, implementation of these guidelines, policies and procedures begins at the investigator and researcher level. In most cases, potential delays in obtaining an opinion on a particular project from the responsible EC are in part due to inappropriate documentation, which in turn is due to lack of knowledge and experience in addressing the ethical issues (73,74). Setting up an internal institutional ethics committee (IEC) holds promise here for not-for-profit organizations, as these internal committees could provide initial feedback on research proposals. This would help them to address critical ethical issues prior to the submission of proposals to regional/ local or national ECs, thus considerably reducing the time taken for obtaining a positive opinion, and saving funds and energy. However, this does not necessarily guarantee approval of proposals by ECs (74). In addition, internal ethics committees can advise on the training of investigators with respect to ethical issues in their field of research.

However, to really get the benefits of an IEC, the organization should ensure that it is comprised of trained individuals that are familiar with research settings. This would not only help them to guide the investigators/ researchers in the preparation of project proposals but would also enable monitoring of ongoing research projects. This would in turn help the institution to identify potential gaps in implementing policies and procedures, and to impose sanctions for violations by investigators. However, the risks associated with these committees are the potential occurrence of conflicts of interest, and the personal likes and dislikes of members (75,76). Studies related to evaluation of the role of IECs are scarce. Further studies in this regard might prove useful in determining their efficacy in non-for-profit institutions in implementing institutional, national and international ethical policies and guidelines in the preparation of research proposals, and also in the conduct of research that might raise ethical concerns regarding safety, wellbeing and rights of human subjects in particular, of experimental animals and the overall environment in general.

Conclusion

Ethical approval of research projects, observational studies and clinical trials is necessary in order to safeguard human rights and wellbeing, and to avoid potential harm to society, religious groups, vulnerable subjects and animals. Ethical review of research projects improves the scientific quality and authenticity of research. However, considerable difficulties are faced by investigators and investors in the process of getting approval for setting up clinical trials or food related research, and this has potentially hampered the progress of this kind of research in countries having multiple regulator ECs at various levels. This necessitates the need for reduction in the number of ECs, improvement of the rules and regulations for ethical requirements in food related research, observational and epidemiological studies, and simplification and standardisation of the procedures for the submission of multicentre and interdisciplinary research projects.

Administrative procedures in the approval and setting up of trials are compromising Italy's reputation for high scientific standards in medicine and clinical research. Implementation of simplified legislation governing clinical trials, reduction in the number of ECs, standardisation of contracts, and improvement of trials management through adequate clinical trials units, can encourage clinical research in Italy.

In addition, review of research proposals prior to submission by internal institutional ethics committees holds the promise of reducing the time duration required for the processing of proposals. However, this does not guarantee a positive outcome from an EC committee review. Reduction in the number of ECs, centralization of submission procedures and further studies evaluating the efficacy of internal ethical committees in setting up and conducting clinical trials in Italy might help in simplifying ethical review procedures and enhancing Italy's competitiveness with respect to the global market for clinical research. The main problem in Italy and Europe is the lack of common legislation that would coordinate all the European countries in the same manner. Furthermore, there are difficulties in the interactions among countries located in different continents due to the high lack of homogeneity among systems. Finally, we took the Italian model as

an example, because an international committee based in Italy is going to be established for the laboratory EBTNA-LAB. In the future, we will produce other works and publications in order to address other issues regarding ethics committees.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Istituto Superiore di Sanità. Tesauro italiano di bioetica. Gruppo di Studio Istituto Superiore di Sanità "Tesauro italiano di bioetica" 2006; x: 132. Available at: http://old.iss.it/binary/sibi/cont/thesa.1151313180.pdf
2. Furlan E. Comitati Etici in sanità: storia, funzioni, questioni filosofiche. Milano: Franco Angeli, 2015.
3. National Committee for Bioethics. I comitati per l'etica nella clinica. 2017. Available at: http:// bioetica.governo.it/media/172155/p127_2017_i-comitati-etici-per-la-clinica_it.pdf.
4. UNESCO. Guide No 1: Establishing bioethics committees. 2005. Available at: http://unesdoc.unesco.org/images/0013/001393/139309e.pdf.
5. De Panfilis L, Merlo DF, Satolli R, Perin M, Ghirotto L, Costantini M. Clinical ethics consultation among Italian ethics committee: A mixed method study. PLoS ONE 2019; 14: e0226710.
6. Rice TW. The historical, ethical, and legal background of human subjects' research. Respir Care 2008; 53: 1325–9.
7. World Medical Association. Declaration of Helsinki: ethical principles for research involving human subjects. 2008. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html.
8. http://www.wma.net/en/60about/70history/01declaration Helsinki/index.html.
9. Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine CETS. 1997. Available at: http://conventions.coe.int/Treaty/Commun/QueVoulez-Vous.asp?NT=164&CM=8&DF=04/02/2013&CL=ENG
10. Charter of Fundamental Rights of the European Union. Off J Eur Union 2010; C83/393.
11. European Commission. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Off J Eur Union 2014; 57: 1–76.
12. Gehring M, Jommy C, Tarricone R, et al. Towards a more competitive Italy in clinical research: the survey of attitudes towards trial sites in Europe (The SAT-EU Study). Epidemiol Biostat Publ Health 2015; 12: 1–9.
13. Veerus P, Lexchin J, Hemminki E. Legislative regulation and ethical governance of medical research in different European Union countries. J Med Ethics 2014; 40: 409-13.
14. Marra L, Clementi ML. Il dibattito bioetico in ambiente laico in Italia e l'esperienza dei Comitati. In: La salute in Italia: Rapporto 1998. Roma: Ediesse, 1998.
15. National Committee for Bioethics. I comitati per l'etica nella clinica. 2017. Available at: http://bioetica.governo.it/media/172155/p127_2017_i-comitati-etici-per-la-clinica_it.pdf.
16. Cattorini P. Bioethics and ethics committees in Italy. The present situation and the perspectives. NTM N.S. 1993; 1: 129–36. https://doi.org/10.1007/BF02914108.
17. Italia. Decreto legislativo 24 giugno 2003, n. 211. Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico. Gazzetta Ufficiale della Repubblica Italiana – Serie generale n. 184, 9 agosto 2003 (Suppl. ord. n. 130).
18. Parlamento Italiano. Legge 8 novembre 2012, n. 189. Conversione in legge, con modificazioni, del decreto-legge 13 settembre 2012, n. 158, recante disposizioni urgenti per promuovere lo sviluppo del Paese mediante un più alto livello di tutela della salute. Gazzetta Ufficiale della Repubblica Italiana – Serie generale n. 263, 10 novembre 2012 (Suppl. ord. n. 201).
19. Ethics committee in Italy: http://www.eurecnet.org/information/italy.html
20. Ministerial Decree February, 8, 2013. "Parameters for the composition and functioning of Ethics committee", GU, 2013.
21. Savonitto S, Coppola T, Braglia P, Ciccone A. [Informed consent for clinical investigation in the critically ill patient. An introduction to the regulation 536/2014/EC on clinical investigation of medicinal products for human use, repealing Directive 2001/20/EC]. G Ital Cardiol (Rome) 2016; 17: 326–34.
22. Petrini C. Some comments on the new regulations governing ethics committees in Italy. Ann Ist Super Sanita 2014; 50: 160-2.
23. Parlamento Italiano. Legge 11 gennaio 2018 n. 3. Delega al Governo in materia di sperimentazione clinica di medicinali nonché disposizioni per il riordino delle professioni sanitarie e per la dirigenza sanitaria del Ministero della salute. Gazzetta Ufficiale della Repubblica Italiana – Serie generale n. 25, 2018.
24. https:// www.moh.govt.nz/ notebook/ nbbooks.nsf/ 0/F21C6588D45EBA67CC257A600009C6C7/ $file/ ethical-guidelines-for-observational-studies-2012.pdf
25. Perlman M. Ethical issues in 'observational research'. Paediatr Child Health 2000; 5: 89-90.
26. Kıraç FS. Is ethics approval necessary for all trials? A clear but not certain process. Mol Imaging Radionucl Ther 2013; 22: 73-5.

27. Italian Ministerial Circular n. 6 *Gazzetta Ufficiale* n. 214, 12.9.2002, Italy – Ministry of Health.
28. AIFA ruling 20.3.2008, *Gazzetta Ufficiale* n. 76, 31.3.2008.
29. Loder E, Groves T, MacAuley D. Registration of observational studies. BMJ 2010; 340: c950.
30. ClinicalTrials.gov. FDAAA 801 Requirements. 2017. Available at: https://clinicaltrials.gov/ct2/manage-recs/fdaaa.
31. Williams RJ, Tse T, Harlan WR, Zarin DA. Registration of observational studies: is it time? CMAJ 2010; 182: 1638-42.
32. ClinicalTrials.gov. ClinicalTrials.gov protocol registration data element definitions for interventional and observational studies. 2017. Available at: https://prsinfo.clinicaltrials.gov/definitions.html.
33. The European Network of Centres for Pharmacoepidemiology and Pharma -covigilance (ENCePP). The European Union electronic Register of Post- Authorisation Studies (EU PAS Register). 2017. Available at: http://www.encepp.eu/encepp_studies/indexRegister.shtml.
34. Boccia S, Rothman KJ, Panic N, et al. Registration practices for observational studies on ClinicalTrials.gov indicated low adherence. J Clin Epidemiol 2016; 70: 176-82.
35. Kıraç FS. Is ethics approval necessary for all trials? A clear but not certain process. Mol Imaging Radionucl Ther 2013; 22: 73-5.
36. Orchard J. For debate: should observational clinical studies require ethics committee approval? J Sci Med Sport 2008; 11: 239-42.
37. Moser B, Röggla G. Should observational clinical studies require ethics committee approval? J Sci Med Sport 2008; 11: 518.
38. Claudot F, Alla F, Fresson J, Calvez T, Coudane H, Bonaïti-Pellié C. Ethics and observational studies in medical research: various rules in a common framework. Int J Epidemiol 2009; 38: 1104-8.
39. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007; 147: 573-7.
40. International Committee of Medical Journal Editors (ICMJE). Preparing for submission. 2016. Available at: http://www.icmje.org/recommendations/browse/manuscriptpreparation/preparing-for-submission.html#d.
41. The BMJ. Ethics approval of research. 2017. Available at: http://www.bmj.com/aboutbmj/resources-authors/formspolicies-andchecklists/ethics-approvalresearch.
42. PLOS ONE. Submission Guidelines. 2017. Available at: http://journals.plos.org/plosone/s/submission-guidelines#loc-observationaland-field-studies.
43. The Lancet. Instructions for Authors. 2017. Available at: http://www.thelancet.com/pb/assets/raw/Lancet/authors/lancet-information-forauthors.pdf.
44. Springer. Publishing ethics. 2017. Available at: https://www.springer.com/gp/authorseditors/journal-author/journal-authorhelpdesk/publishing-ethics/14214.
45. Godfray HCJ, Beddington JR, Crute IR, Haddad L, Lawrence D, Muir JF, Toulmin C. Food security: the challenge of feeding 9 billion people. Science 2010; 327: 812-8.
46. Gostin LO. Public Health Law and Ethics: A Reader. Berkeley, University of California Press, 2010.
47. Ethics and food-related research – a guidance note: European Commission FP7 Ethical Rules, 2012.
48. EU Regulation 1924/2006. Available at: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1924:20080304:EN:PDF
49. FAO practical guide: basic concepts of food security, FAO, Rome. 2009.
50. Hartmann M. Impact assessment of the European Clinical Trials Directive: a longitudinal, prospective, observational study analysing patterns and trends in clinical drug trial applications submitted since 2001 to regulatory agencies in six EU countries. Trials 2012; 13: 53.
51. Perrone F, Marangolo M, Di Costanzo F, et al. Insurance for independent cancer trials. Ann Oncol 2004; 15: 1722–3.
52. Gehring M, Taylor RS, Mellody M, et al. Factors influencing clinical trial site selection in Europe: the survey of attitudes towards trial sites in Europe (the SAT-EU Study). BMJ Open 2013; 3: e002957.
53. Brown L. Major changes to clinical trials regulation in the EU. Appl ClinTrials 2014.
54. Kenter MJ, Cohen AF. Re-engineering the European Union clinical trials directive. Lancet 2012; 379: 1765–7.
55. Petrini C. Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use: an overview. Istituto Superiore di Sanità, 2014. Available at: http://www.scielosp.org/pdf/aiss/v50n4/04.pdf
56. Clinical research in Europe–trials and tribulations. Lancet 2012; 379: 1764.
57. Gehring M, Jommy C, Tarricone R, et al. Towards a more competitive Italy in clinical research: the survey of attitudes towards trial sites in Europe (The SAT-EU Study). Epidemiol Biostat Publ Health 2015; 12: 1–9.
58. Agenzia Italiana del Farmaco. La sperimentazione clinica dei medicinali in Italia, 12 Rapporto Nazionale. 2013. Available at: https://www.agenziafarmaco.gov.it/ricclin/sites/default/files/files_wysiwyg/files/Pubblicazioni_OsSC/13_Rapporto_OsSC_2014%20(2).pdf
59. Sexton J. State of the world's science. Sci Am 2012; 36–40.
60. Analysis of Clinical trials listings for Germany, France, Italy, UK, Spain, NL, Belgium, Switzerland, and Austria on the NIH database. 2012. Available at: http://clinicaltrials.gov
61. Porcu L, Poli D, Torri V, et al. Impact of recent legislative bills regarding clinical research on Italian ethics committee activity. J Med Ethics 2008; 34: 747–50.
62. Hernandez R, Cooney M, Dualé C, et al. Harmonisation of ethics committes' practice in 10 European countries. J Med Ethics 2009; 35: 696–700.
63. EFGCP Report. The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe and Beyond. 2012. Available at: http://www.efgcp.eu/EFGCPReports.asp?L1=5&L2=1.
64. Gehring M, Taylor RS, Mellody M, et al. Factors influenc-

ing clinical trial site selection in Europe: the survey of attitudes towards trial sites in Europe (the SAT-EU Study). BMJ Open 2013; 3: e002957.
65. Analysis of Clinical trials listings for Germany, France, Italy, UK, Spain, NL, Belgium, Switzerland, and Austria on the NIH database. 2012. Available at http://clinicaltrials.gov
66. Gehring M, Jommy C, Tarricone R, et al. Towards a more competitive Italy in clinical research: the survey of attitudes towards trial sites in Europe (The SAT-EU Study). Epidemiol Biostat Publ Health 2015; 12: 1–9.
67. Jommi C, Paruzzolo S. Public administration and R&D localisation by pharmaceutical and biotech companies: a theoretical framework and the Italian case-study. Health Policy 2007; 81: 117–30.
68. De Feo G, Frontini L, Rota S, et al. Time required to start multicentre clinical trials within the Italian Medicine Agency programme of support for independent research. J Med Ethics 2015; 41: 799–803.
69. McMahon L, Cagnazzo C, Campora S, et al. The invisible hand of Clinical Research Coordinators in supporting oncology clinical research in Italy. I Supplementi di Tumori. 2014; 15: F45.
70. Cagnazzo C, Nanni O, Campora S, et al. Clinical Trials Units in Italy: the perception of the Clinical Research Coordinators. Ann Oncol 2016; 27: iv111–2.
71. Giannuzzi V, Altavilla A, Ruggieri L, Ceci A. Clinical trial application in Europe: what will change with the new regulation? Sci Eng Ethics 2016; 22: 451–66.
72. Cagnazzo C, Campora S, Ferretti E, Arizo F, Marchesi E. New European Clinical Trial Regulation: perception and expectations in Italy. Ann Oncol 2017; 28: 1648-54.
73. De Feo G, Chiabrando G, Cannovo N, Galluccio A, Tomino C. Harmonization of the practice of independent ethics committees in Italy: Project E-submission. PLoS One 2012; 7: e48906.
74. Dixon-Woods M, Foy C, Hayden C, et al. Can an ethics officer role reduce delays in research ethics approval? A mixed-method evaluation of an improvement project. BMJ Open 2016; 6: e011973.
75. Wolf LE, Zandecki J. Conflicts of interest in research: How IRBs address their own conflicts. IRB 2007; 29: 6–12.
76. Shetty YC, Marathe PA, Billa GV, Nambiar CP. A study to assess completeness of project application forms submitted to Institutional Ethics Committees (IEC) of a tertiary care hospital. Perspect Clin Res 2012; 3: 133–8.

Received: 3 September 2020
Accepted: 14 October 2020
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