LIBRO DE PONENCIAS Y COMUNICACIONES

EUROPEAN CONGRESS OF RESEARCH ETHICS COMMITTEES

EUREC-ANCEI joint Conference

4 CONGRESO ANCEI

May 17-19, 2017 Barcelona, Spain

Institut Borja de Bioètica
UNIVERSITAT RAMON LLULL

Asociación Nacional de Comités de Ética de la Investigación

Sant Joan de Déu Research Foundation

IMAGEMEND

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Presentación

Apreciados miembros de Comités de Ética de la Investigación:

Esta carta no solo se dirige a los miembros de los Comités de Ética de la Investigación sino también a cuantas personas en España y en Europa están interesadas en la Bioética y en la investigación. En este año se han producido importantes acontecimientos en el campo de la Bioética. En particular merece la pena mencionar el inicio de la implementación en diversos países europeos del Reglamento UE 536/2014. Sobre los ensayos clínicos de medicamentos de uso humano, la WMA ha presentado también la "Declaración de Taipei sobre las Consideraciones Éticas sobre Bases de Datos de Salud y Biobancos" y el Consejo de Europa ha adoptado su Recomendación CM/Rec (2016) del Comité de Ministros a los Estados Miembro, sobre la investigación con materiales biológicos de origen humano.

Todos estos acontecimientos se han producido en un entorno político en que la idea de la Unión Europea parece sacudida y los Comités de Ética de la Investigación han sido marginados por la legislación europea, en vez de prestarles la atención necesaria por su importante contribución en asegurar la adecuada protección a los sujetos humanos que participan en los ensayos clínicos. En estas circunstancias es muy importante buscar consensos que afiancen el futuro de la ética de la investigación en seres humanos y que puedan abrir nuevos caminos de pensamiento para una investigación cooperativa en Europa.

A tal fin se ha organizado el presente Congreso conjunto EUREC-ANCEI (*European Network of Research Ethics Committees* - Asociación Nacional de Comités de Ética de la Investigación) en el que en sucesivas sesiones de mesas redondas y ponencias se tratará:

1. La propuesta de una plataforma conjunta de evaluación ética de la investigación, sea esta biomédica o no, de la mano del proyecto SATORI de la Unión Europea.
2. La Recomendación CM/Rec (2016) del Comité de Ministros Europeo, a los Estados Miembro sobre la investigación con materiales biológicos de origen humano.
3. La temática de las relaciones intergeneracionales de la mano de proyectos europeos y las tensiones psicológicas que se plantean en la adolescencia.
4. El significado y las implicaciones de la independencia de los Comités de Ética de la Investigación.

5. El impacto del Reglamento UE 536/2014 sobre los Comités de Ética de la Investigación de la mano de ejemplos en varios países europeos, pros, contras, excesos y carencias.
6. La ética de la investigación en la secuenciación y predicción de la evolución en pacientes con alto riesgo de alteraciones psiquiátricas, incluyendo niños y adolescentes (IMAGEMEND Project).
7. La investigación en poblaciones vulnerables y la participación de las mismas en la evaluación ética. El proyecto *Kids* Barcelona.
8. Debate sobre el tipo de Comité de Ética de la Investigación que sería adecuado para Europa. ¿Comité de proximidad o de regulación administrativa?
9. Problemas éticos en la investigación con dispositivos sanitarios *(medical devices)*, el proyecto de nuevo reglamento europeo. El ejemplo de la cirugía fetal.
10. Para facilitar la expresión de opiniones europeas y recoger el pensamiento sobre los conceptos planteados, se ha programado una sesión de Comunicaciones a los distintos temas del Congreso.
11. El futuro de los Comités de Ética de la Investigación, perspectivas y esperanzas: conclusiones del Congreso.

El Congreso se celebra en el Auditorio del Hospital Universitario Sant Joan de Déu de Barcelona que colabora también en su organización con el Institut Borja de Bioètica de la Universidad Ramon Llull. El Comité Organizador espera que este acontecimiento sea una ocasión para el intercambio de ideas y el debate bioético. Un foro que permita prever líneas de futuro, por lo que anima a todas las personas interesadas en la Bioética y en la Investigación, Biomédica o no, a participar en él y también en disfrutar de unos días de la primavera de Barcelona.

Muchas gracias todos.

Mª Concepción Martín Arribas

Presidenta de ANCEI

Presentation

Dear members of Research Ethics Committees,

This letter is not only addressed to the members of Research Ethics Committees, but also to every person, either in Spain or in the rest of Europe, who is interested in Bioethics and research. In the course of the last year a lot of very important events in the realm of Bioethics have occurred. In particular it is worth mentioning the implementation of the new EU Regulation 536/2014 on clinical trials on medicinal products for human use in EU Member States, WMA also introduced its "Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks", and in addition "Committee of Ministers" of the Council of Europe, adopted its Recommendation CM/Rec (2016) of the Committee of Ministers to member States on research on biological materials of human origin.

All these issues came about in a political environment where the idea of the European Union seems to be shaken and where Research Ethics Committees were marginalized by the European legislature rather than given the necessary attention to their important contribution to ensuring the protection of human subjects in clinical trials. In light of these circumstances, it is very important to look for consensus that can consolidate the future of the ethics of research on humans and can open new ways of thinking for a cooperative research in Europe.

With these targets in mind the Barcelona EUREC-ANCEI (European Network of Research Ethics Committees – Asociación Nacional de Comités de Ética de la Investigación) Conference has been organised, with lectures, round tables and presentations. They will tackle the following topics:

1. The proposal of a new joint platform for research ethics evaluation, either biomedical or not, by means of European projects.
2. The "Recommendation CM/Rec (2016) of the Committee of Ministers to member States on research on biological materials of human origin" and the personal data handling in this context and Biobanks.
3. The features of generational relationships by means of European Projects which treat the psychological stress on adolescents.
4. The meaningfulness and implications of the Research Ethics Committees' independence.

5. The impact of the new EU Regulation 536/2014 on the Research Ethics Committees of different European countries. Description, pros, cons, surfeits and deficits.
6. Ethics of research on sequencing and prediction in patients with high risks of psychiatric disorders including children and adolescents (the IMAGEMEND project).
7. The research in vulnerable populations. The participation of children in the Research Ethics Committees. The Kids Barcelona Project.
8. The question of what kind of Research Ethics Committee can fit in Europe. A proxy committee or an administrative regulator one.
9. Medical devices: the new regulatory project. Ethical problems in the clinical trials and use of medical devices. The example of fetal surgery.
10. To get European opinions and feedback about the proposed topics a free communications session on the different topics of the conference have been programmed.
11. The future of Research Ethics Committees, perspectives and hopes.

The Conference takes place in the auditorium of SJD Barcelona Children's Hospital, and the Borja Institute of Bioethics of the Ramon Llull University will also collaborate in the organisation of the event. All organisers of the EUREC-ANCEI Joint Conference hope it will be an occasion for exchanging ideas and bioethical debate. An event to foresee the growing lines of the future, where all people interested in Bioethics and in Research, either Biomedical or otherwise, are invited to participate, whilst enjoying the beauty of Barcelona in the springtime.

Thank you very much to all.

Mª Concepción Martín Arribas

Presidenta de ANCEI

PROGRAMA / PROGRAM

Wednesday the 17th May 2017

Studies with minors and adolescents or children on schizophrenia, bipolar disorder and attention deficit-hyperactivity disorder: Results and ethical Challenges of the IMAGEMEND project

08:00-09:00 Registration

09:00-09:15 Elmar Doppelfeld (Chair of EUREC): Introduction

09:15-10:00 The IMAGEMEND Project and its Delphi studies on attitudes and ethical views of patients, relatives, health care professionals in IMAGEMEND
Marcella Rietschel/Jana Strohmaier
Discussion

10:00-10:45 From clinical data to population-based direct recruitment: The beauty and hardship of register data recruitment
Christina Hultman
Discussion

10:45-11:00 Coffee Break

11:15-12:00 Data collection of minors in Research in IMAGEMEND
Jan Buitelaar
Discussion

12:00-12:45 Ethical issues on testing children and challenges for RECs
Dirk Lanzerath
Discussion

13:00-14:50 Lunch Break

15:00-15:45 Biobanks and Data Protection
Javier Arias-Díaz
Discussion

15:45-16:30 Panel

16:30-16:45 Coffee Break

16:45-17:00 Report on recent developments of EUREC
Elmar Doppelfeld (Chair of EUREC) & Dirk Lanzerath (Secretary General of EUREC)

17:00-17:30 Information Technologies and Ethics in Medical Research
Albena Kuyumdzhieva (European Commission)

17:30-18:00 Ethics assessment and guidance in social sciences and humanities: Findings of the SATORI project
Rok Benčin (Research Fellow, Institute of Philosophy, Research Centre of the Slovenian Academy of Sciences and Arts, Ljubljana, Slovenija)

18:00-18:20 Towards a unified ethics assessment procedure for non medical research in Greece
Panagiotis Kavouras (National Technical University of Athens, Greece)

18:20-18:30 Final Remarks
Elmar Doppelfeld (Chair of EUREC)

18:30 End of EUREC Ordinary General Meeting *(public part)*

18:30-18.50 General Assembly Meeting *(only for EUREC Members)*

Thursday the 18th May 2017

08:00-09:00 Registration

09:00-09:30 Opening and Welcoming

09:40-10:15 Opening Main Lecture
Meaningfulness and implications of the Research Ethics Committees Independence
Prof. Gianni Tognini

10:30-10:50 Coffee Break

10:50-12:20 First Round Table **"The impact of the new UE Regulation 36/2014 on the RECs of different European countries. Description, pros, cons, surfeits and deficits"**
Moderator: César Hernández García. Jefe del Departamento de Medicamentos de Uso Humano de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)
Speakers:
- Sylvie Hansel Esteller (France)
- Marina Ferri (Italy)
- Joerg Hasford (Germany)
- Jozef Glasa (Slovaquia)

12:20-13:00 Discussion

13:00-14:15 Lunch

14:15-15:45 Second Round Table **"What kind of REC can fit in Europe?"**
Moderator: Monserrat Esquerda. Director of Borja Institute of Bioethics of Barcelona
Speakers:
- Dirk Lanzerath (Germany) – Secretay General of EUREC
- Bernabé Robles (Spain)
- Eugenijus Gefenas Lithuanian Bioethics Committee (LBEC) and EUREC Vice Chair
- Michael Bone (United Kingdom)

15:45-16:15 Discussion

16:15-16:40 Coffee Break

16:45-18:15 Third Round Table **"Research in vulnerable populations. The participation of children in the RECs."** The Kids Barcelona
Moderator: Nuria Terribas (Grifols Foundation - Spain)
Speakers:
- Joana Claverol (SJD Foundation - Spain)
- A child of Kids Barcelona Project
- Pirkko Lepola (EMA - Finland)
- Kate Harvey (Nuffield Council – UK)

18:15-18:30 Discussion

18:30-19:30 ANCEI Assembly-Only for members

20:00 Congress Dinner - Restaurant to be selected

Friday the 19th May 2017

09:00-10:15 Fourth Round Table **"Ethic problems in the clinical trials and use of medical devices. The example of fetal surgery"** - What may bring the next European Regulation?
Moderator: Pablo Ferrer Salvans (Spain)
Speakers:
- Xavier Canals (Spain)
- Eduard Gratacós. Saint John of God Hospital (Spain)
- Saskia de Weerd-Hamer (Netherlands)

10:15-10:30 Discussion

10:30-10:45 Coffee Break

10:45-13:00 Fifth Round Table **"Communications"**
Moderator: Coloma Moreno Quiroga (ANCEI)

13:00-13:40 Closing Lecture **"The Future of RECs, perspectives and hopes"**
Prof. Elmar Doppelfeld (Chair of EUREC)

14:00 Conclusions of the Conference

Closing of the conference

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MESA: **"What kind of REC can fit in Europe?"**

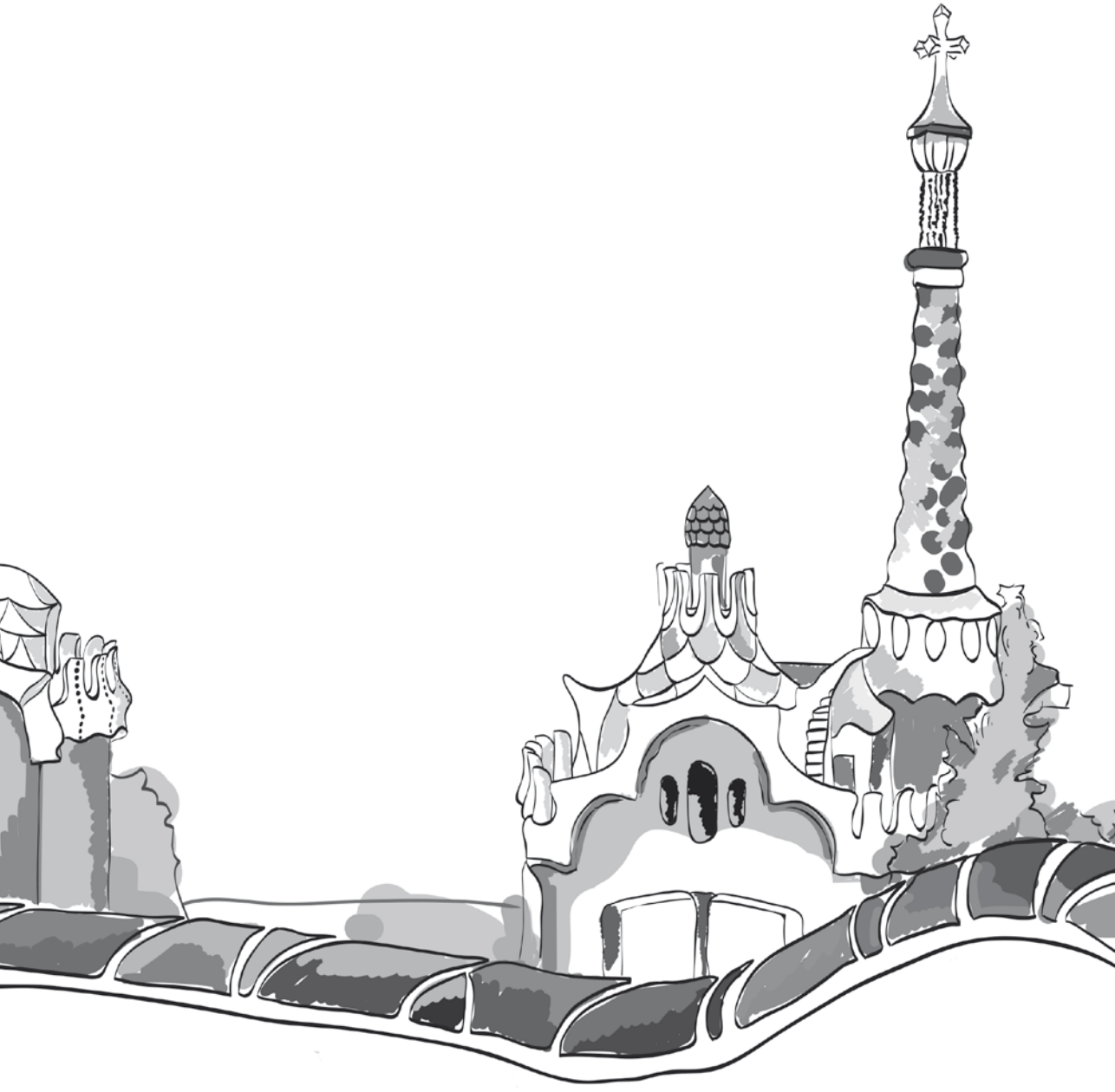
MESA: "Research in vulnerable populations. The participation of children in the RECs" The Kids Barcelona

MESA: "Ethical problems in the clinical trials and use of medical devices. The example of fetal surgery" What may bring the next European Regulation?

COMUNICACIONES

POSTERS

CONFERENCIA DE CLAUSURA



CONFERENCIA INAUGURAL

Meaningfullness and implications of the Research Ethic Committees independence

Gianni Tognoni
IRCCS Istituto di Ricerche Farmacologiche "Mario Negri" - Milano, Italy.

INTRODUCTION

The framework which could justify the solemn wording of the title given to this presentation could be summarized as follows: we are living in a time where research ethical committees are under strong, generalized pressure to become a formally efficient bureaucratic instrument and the most advanced and ambivalent marker of the ongoing process of transformation of health care into a component of the global market of goods; such "evolution" requires that the presence and the rights of human subjects become variables *declared* to be the protagonists and the goal of research, provided that they are *dependent* variables.

This long statement could appear at a first sight as a provocative affirmation of a biased a priori position. It is however a rather obvious, mandatory, objective mirror of the debates which occupy, with endless editorials comments since at least five years (at the frontier between the disappointing conclusion of the MDG, and the slow-controversial implementation of the SDG) the scientific (medical and economic) literature, as well as the planning documents of the international agencies. It is not here the place to provide detailed references: they are readily available to all who follow (and certainly this is the case of the members of ethical committees) at least the major medical journals.

The purpose of these notes is not in fact to provide another contribution to the ongoing debates and controversies, but to suggests some practical "points of view" on the central question formulated in the title: could, and how, the main goal of research ethical committees (REC) – to play an independent role with respects to the various actors and the scenarios suggested above – be preserved, and possibly promoted?

The challenge of sharing some elements which could be useful for the formulation of a not easy answer is developed in three steps:

a) A brief historical recognition of the key words, and corresponding "institutions", which have accompanied and characterized the development of REC in medicine and in society;
b) The indication of some markers which could be considered concrete expression of the independence of REC;
c) Few operational proposals which could favour the restitution to REC of their role of independent actors in the conflicting scenarios of the present evolution of health care systems, which are at the frontier between an identity of health as indicator-promoter

TABLE 1. Protagonists of the evolving-conflicting relations of definitions and scenarios.

1	Institutional Review Boards (IRB)
2	Regulation(s) for drug approval: FDA
3	Helsinki Declaration
4	Research independence, and public health oriented statistics / methodology
5	GCP - ICH
6	The confounding use of the term "ethics"/EC in regulatory documents
7	Oviedo vs EMA
8	WTO vs PP vs Conflict of interest
9	Independence from vs independence for
10	The competence(s) and the weight of EC decisions

of the human rights to life, and its transformation into a principally economically sustainable component of a market-driven development.

Each of the three steps is synthetized in a Table whose key terms of reference are briefly commented.

According to the by now classical criteria, an introductory note must include the declaration of personal conflicts of interests, which coincide in this case with the personal professional biases. A long-term full time involvement in clinical research, mainly in clinical pharmacology and epidemiology, methodology and implementation of randomized clinical trials, parallel activity (since 1978) in institutional, regional, national REC and drug legislation, a long term activity in international NGOs working in the area of human and peoples' rights.

A BRIEF HISTORICAL REMINDER OF THE ROLES AND GOALS OF REC

Table 1 proposes terms and steps which are obviously well known for all those working in REC. Few brief comments are possibly useful however, by framing them according to the different contexts, actors, goals, which are part of the overall development of:

- On one side the ethical values and the normative and cultural steps which are listed chronologically;
- On the other side the role of the actors of research.

The Sixties are the time framework of the three first steps, confronted principally with the objective of assuring the safety, even more than the efficacy component of the first era of drug development. IRBs, FDA, Helsinki are the expression of the coincidence between independent professional responsibilities and normative public agencies. The Helsinki Declaration becomes the ethical, non-normative symbol and instrument and term of reference, substantially consistent throughout its periodical revisions. The background of its value may be seen in the fact that it assumes as a solid and agreed principle that research on/with drugs (at the time the most promising and rapidly developing expression of medical

progress) is, and cannot be other than, expression of an health care where the strict coincidence between the interests of patients and society, and those of the medical profession is a non-disputable code of conduct.

Point 4 of the Table summarizes the most productive decades (70-80) of the development of a flexible and rigorous RCT methodology, which assures the most significant progresses in critical fields of medicine (from cardiovascular to oncology), with specific focus on clinically and public health relevant outcome end-points: statistics is a support for the principal objective of producing results on survival advantages documented in population trials which bridge efficacy to effectiveness: drugs are a variable to test and provide responses to unmet needs under the responsibility of steering committees whose independence from public and private sponsors is a must.

The Nineties (point 5) represent a drastic turn: registration of commercially available products concentrates the attention on the formal, not substantial, quality of research and data. The GCP-ICH normative is prepared with the rigorous exclusion of those researchers who have shown the productivity of their independence and their capacity of creating independent control bodies (e.g. DSMC). The growing importance of market pressures (which coincide with the establishment of the WTO in 1994) and of conflicts of interest become the real protagonists, as well as the focus of the increasingly heavy rules of ICH-GCP (never proven to be effective in improving the quality of research). EC are mentioned in the ICH-GCP without any reference to the clinical relevance of the research, and are directed to assure a administrative compliance with the procedures (despite the parallel growing in medicine and society of bioethical interests).

The points 6, 7, 8 underline some of the best known situations of conflict, and even more worrying separation, between measures aimed to protect-develop a rights centered approach, and debates on the need to protect the Private exigencies of industrial actors vs the Public concerns for an independence in the name of public health (the independence "for" of point 9). The pressure to transform EC in bureaucratic steps to favour rapid approvals of protocols is clearly at the center of ongoing market oriented proposals for the "new" roles of EC.

EC decisions (point 10) have hardly to do with the contents of research: they are concentrated in the evaluation of procedures which correspond to the operational components of the protocols, and to the formulation of informed consents which are widely recognized not to comply with a patient-centered and tailored information for never culturally and contextually "standard" patients.

WHY AND HOW AN "INDEPENDENCE FOR"

The five points proposed in Table 2 are formulated within the framework which has been developing over the last 15 years and which is abundantly documented in the literature related to the changing world of RCT (the long series of articles published in the NEJM from July 2016 is one of the most complete summaries of the key issues).

According also to the fundamental criteria of the planned European legislation, EC are requested to be functional to research scenarios where the public investment is assumed to

TABLE 2. Indicators of "independence for".

1	EC as promoters of research
2	Public funding of functioning ECs and transparency of decision processes
3	Drug control(s) for registration purposes as a "marginal" model of research, culture, accountability (see point 7 above)
4	Drop "informed consent": a basic step to allow-develop a language/practice/culture of personal/human rights
5	Representativeness of scenarios of care

be marginal, with respect to a drug-targeted (non problem-oriented) activity, where rapid registration of new products is the almost exclusive goal (irrespective of the growing evidence that, with major, though very few, exceptions, the unmet health needs are recognized as the true negleted priority).

Confronted with the above scenarios a passive attitude of acceptance of ICH-GCP tailored EC may appear inevitable: ethical (i.e.: patient-populations-needs centered) considerations are bound to remain at the level of wishful thinking and/or of marginal realistic adaptations to the exigences of the market (for drugs and devices).

An alternative view could have a stimulating starting point in the growing perception that research should be interested in strategies of care, more than on specific "new" drug. EC should re-discover their REC identity, to represent the rights to health of the populations, even more in the present development of the various versions of "precision medicine".

The points of Table 2 are in this sense a tentative of "resilience", the least to remind what could coincide with an "independence for": they could be part of a struggle-experimentation for an identity which include:

a) The self-consciousness and the shared agreement that REC do not have a primary role of control, but of promoting-assuring clinical and public health relevant research;
b) The collective function of REC must be recognized as a public investment, not as a burden for public structures, which become sustainable only with the fees of industrial sponsors;
c) The disclosure of the decision processes of REC, should become an instrument of permanent information of the medical and public opinion, to remind that the terms of reference of research are not the trials for registration of drug, but the research protocols dictated by the unmet needs;
d) The marginalization of the present informed consent forms, and the development and experimentation of information practices which assure, flexibly, a true understanding and participation of patients;
e) To drop the debates on the "number" of EC, in favour of assuring RECs which update the old IRBs, whose roots were in their capacity of being representative and interacting actors of the caring communities.

The points of Table 2 assume and propose that REC perceive and manage themselves as one of the networks who take the responsibility, and promote the visibility of a research whose quality is proportional to the capacity of addressing in full transparency, the prob-

TABLE 3. Proposals.

1	Let's test reciprocal EC transparency and dialogue on controversial/conflicting issues in a multicentre pilot exercise
2	Cross-check competences and decisions on significant vs relevant vs legitime outcome end-points (and "information"?) in oncology, psychiatric/behavioursal problems, emergency care
3	Alliance with groups who resist useless bureaucracy and promote "research independence"

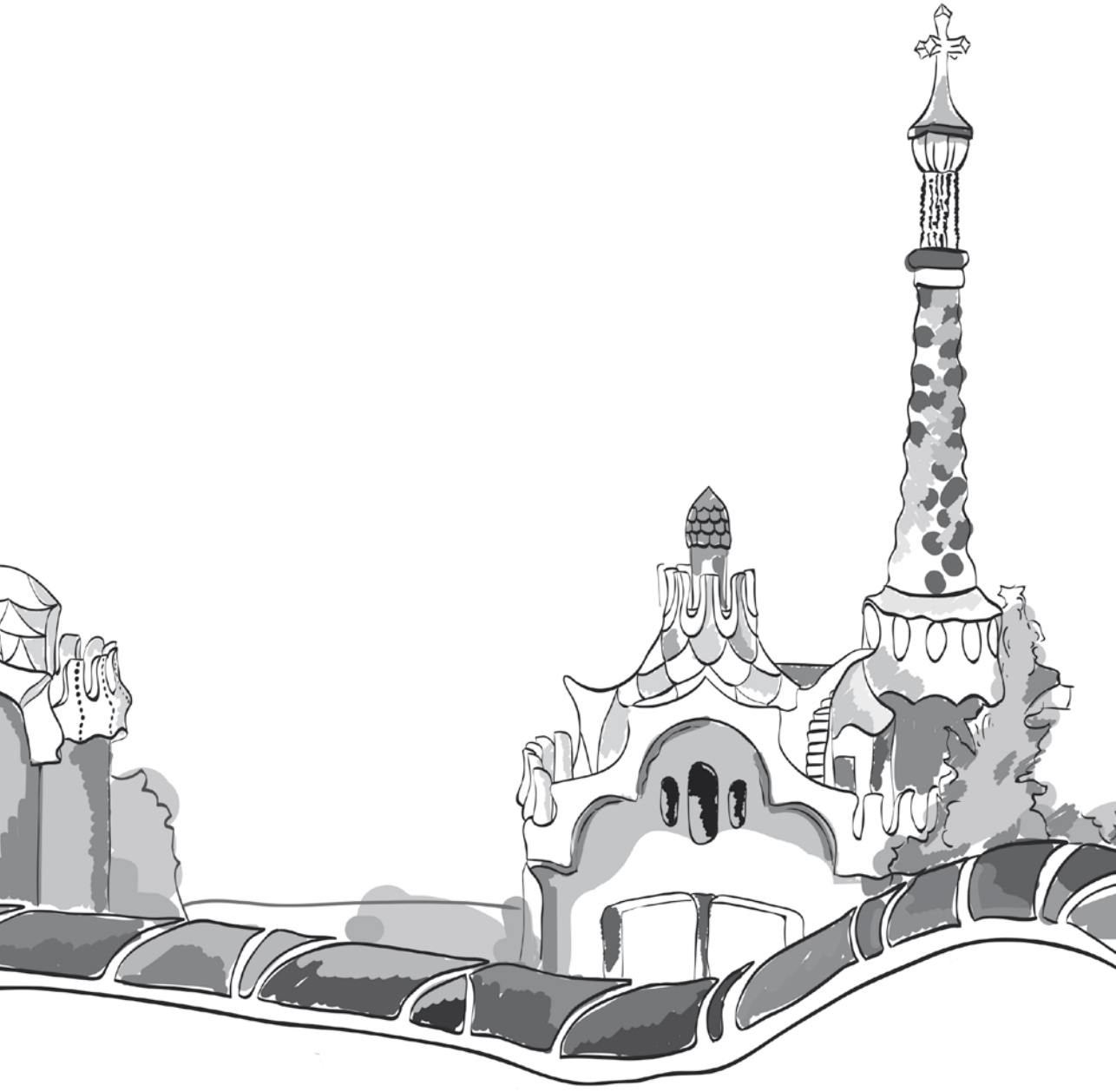
lems which are orphans of attention (from rare diseases to widespread conditions such as Alzheimer dementia and mental disorders).

PROPOSALS

If the REC must have a future, they should aim to become concretely a research network. Table 3 imagines – to avoid being confined and trapped in ir-relevant controlling roles – that some of the many local or tentative experiences presented in this meeting (my personal bias and present affiliation certainly underline the approach of Ricerc@) could become pilot European multicentre programs.

It should be possible to think on network(s) of REC who agree to confront and compare their practices in the evaluation of protocols:

a) To produce collaborative reports where the variability of opinions is presented not as an hindrance, but as a resource: for critical remarks, as well as for propositive ameliorations, both with respect to the definition of outcome end-points, and to the promotion-implementation of strategies of information; where "forms of consent" are downplaid to an administrative (legally valid?) documentation that intelligence and time for a true information process has been assured;
b) To adopt as testing fields some of the most stimulating and critical areas of research so that the judgments on the protocols (oncology is a model areas; but "fragile" patients and populations must be given also priority) could be transformed into collaborative scientific contributions, which document the good and the bad characteristics of the ongoing (public and private) research, and which underline the uncertainly of the evidences, as a potent stimulus for a true participation of investigators and patients;
c) To join – as a network representing REC as allies and promoters of research, and not a boring obstacle – the various groups of investigators who are also looking for a renewed independence, and do not accept to wait passively other, mainly administrative, and inevitably regressive, legislations.



PONENCIAS

1 The impact of the new UE Regulation 536/2014 on the RECs of different European countries. Description, pros, cons, surfeits and deficits

Sylvie Hansel-Esteller

REC / CPP South Mediterranean IV – Montpellier, France. CNCP National Conference of CPP (Committees of Protection of Persons). France.

SUMMARY OF THE SITUATION OF REC IN FRANCE FROM 1991 TO NOVEMBER 2016

Research Ethics Committees in France are named Committees of Protection of Persons CPP.

They have a sustained experience since 1991 date of implementation of the law: *"Law Huriet-Serusclat about the protection of the persons who participate to a biomedical research"* which established 43 REC/CPP with single opinion for France.

Then 40 CPP after Public Health Law 2004 implementing European directive 2001/20/CE and since 2012: 39 CPP over France divided up into 7 regions. There are 5 or 6 CPP by region with regional competence and a national competence (single opinion) for multi-centre trial.

The REC/CPP are approved for 6 years by ministry of Health. They are competent for all interventional clinical researchs: medicinal products for human use, medical devices, cosmetics... and other interventional studies in: physiology, psychology, genetics... and for current care researchs

The composition of each committee includes 14 members titulars and 14 substitutes divided into two medical and societal colleges. The quorum requires 7 persons including a methodologist and a patient association member.

Each committee reviews about 5 or 6 clinical trials forms and about 20 substantial amendments by meeting, monthly.

The sponsor submits his application form to one of the competent committee (by region) according to the location of investigator or coordinating investigator.

Opinions must be justified. In case of negative opinion there is an appeal procedure close to ministry of health for the designation of another committee for a new opinion.

The REC/CPP are fully independent.

The fields of expertise between Research Ethics committees and National competent authority are clearly separated by the law in 2004 and a decree in 2006. Their tasks and responsibilities are well defined. During assessment of a dossier there are exchange of information and transfer of REC opinion and NCA authorization.

TABLE 1.

REC assessment	NCA Assessment
• Ethical, scientific and methodological considerations • Benefits and risks ratio • Protection of trial subjects – Protection of human rights, dignity and wellbeing of persons – Subject information and consent – Recruitment procedure – Indemnities/compensation/insurance • Trial centre: quality of the facilities • Qualification and suitability of investigators and staff...	• Pharmaceutical conformity, quality, security and safety of investigational medicinal products • Security and conformity of methods and practices • Security of subjects: safety monitoring...

NEW SITUATION SINCE NOVEMBER 2016

According to the new UE Regulation 536/2014 and the consequences of "Rennes Accident" in January 2016, Ministry of health proceed to a new regulation which cover all research involving human subjects:

– Ordonnance n° 2016-800 of 16 june 2016 on research involving human subjects modifying the law n° 2012-300 of 5 march 2012 relating to research involving the human subjects https://www.legifrance.gouv.fr/eli/ordonnance/2016/6/16/
– Decree n° 2016-1537 of 16 november 2016 relating to research involving the human subjects. https://www.legifrance.gouv.fr/eli/decret/2016/11/16/
– Several ministerial orders about application form for each type of health research to be submitted to the REC/CPP.

This new regulation creates a lot of change for REC/CPP.

There are no changes concerning the number of REC/CPP, the form and duration of agreement by ministry of Health, the composition, the statute and the funding.

The major changes concern:

– The creation of a National Commission for Research Involving the Human Subjects, attached to the ministry of health, whose missions are, among others, to coordinate and appraise CPP, harmonize their practices and training, to insure exchanges between RECs/CPP and sponsors and between committees and NCA/ANSM, etc.
  The Composition include 21 members whose 8 members of CPP and 14 qualified persons appointed by ministry of Health.
– The functionning of REC/CPP and rules of procedures
– The area of expertise and assessment

DESCRIPTION OF CHANGES FOR REC/CPP

– Extension of the field of competences: CPP must give an opinion on 3 categories of health research:

- 1st category: Interventional studies require opinion of CPP and Authorisation of NCA.
- 2nd category: Interventional studies with low risks and constraints require opinion of CPP.
- 3rd category: Non interventional studies require opinion of CPP.

– **Submission modalities:** No more regional competence but only national competence for each CPP.
The sponsor no longer chooses the CPP/REC but the CPP/REC is designated by randomisation by a national secretary (ministry of health).
In the future, it is expected that the sponsor will not know the CPP/REC and there will be no more relations between sponsor and CPP/REC. Exchanges will be insure by the secretary of National Commission. Sponsor will only have contact with National Competent Agency (ANSM).
– France has chosen to follow the proposed attribution by default by European Regulation 536/2014:
  - Part I Scientific: only NCA-National Competent Agency (ANSM).
  - **Part II Ethical review: CPP/REC.**

  Reminder the EU Regulation:"The ethical review shall be performed by an ethics committee in accordance with the law of the Member State concerned. The review by the ethics committee may encompass aspects addressed in Part I of the assessment report for the authorisation of a clinical trial as referred to in Article 6 and in Part II of that assessment report as referred to in Article 7 as appropriate for each Member State concerned".
  The RECs/CPP are no more involved in the assessment of part I of the application dossier. The part I is only assessed by NCA/ANSM. The assessment of part II remains in the only competence of the REC/CPP.
– **New assessment basis by REC/CPP**
  - Part II: UE Regulation 536/2014 for research on Medicinal products for human use.
  - Part II: French regulation for all research on other health products (medical devices for example...).
  - Part I and Part II: French regulation for all research involving human subjects excepted medicinal products and other health products.

There by, the assessment of scientific and methodological aspects and the benefits/risks ratio falls entirely within the NCA/ANSM.

TABLE 2.

REC/CPP assessment	NCA Assessment
• Ethical considerations • *Scientific and methodological considerations* • *Benefits and risks ratio* • Protection of trial subjects • Protection of human rights, dignity and wellbeing of persons • Subject information and consent • Recruitment procedure • indemnities/compensation/insurance • Trial centre: quality of the facilities • Qualification and suitability of investigators and staff....	• Pharmaceutical conformity, quality, security and safety of investigational medicinal products • Security and conformity of methods and practices • Security of subjects: safety monitoring...

- **Safety assessment:** During clinical trial, RECs/CPP will no longer receive any information about adverse events, adverse drug reactions, serious adverse drug reactions and SUSARs and new security events except for Phase 1 studies.
- **REC/CPP are no more fully independent:** concerning organization, functioning and financial aspects, they are totally dependent of National Commission for Research Involving the Human Subjects (NCRIH) and Ministry of Health. Concerning process and evaluation of clinical research, they are under tutorship of National Competent Authority ANSM.

PROS OF THE EU REGULATION

The main contributions of the EU Regulation concern the following aspects:

- Simplification and standardization of the procedures in Europe.
- Harmonization of the submission dossier and theoretically of practices but concerning only the evaluation of Part I.
- Proportionality of requirements based on risk.
- Possibility of co-sponsoring.
- Simplification of Vigilance rules.
- Transparency of trials and results.

CONS OF THE EU REGULATION

The worst disadvantage is the separation between scientific and ethical issues.

The only involvement of RECs in the evaluation of Part II and their exclusion in the assessment of Part I, implies: no assessment of the risks and benefits for the participants, no assessment of scientific and methodological aspects namely the relevance of the trial.

In new French regulation, the absence of pharmacovigilance information to the REC/CPP will no longer insure quality and update of informed consent and protection of participants.

Within international recommendations and French regulation, RECs are assigned to ensure protection, dignity, rights, well-being and safety of persons involved in a research. The possible restrictions of EU Regulation do not contribute to this purpose.

The ethical principles included in the French regulation cannot be fulfilled by REC/CPP: *" No research involving the human person can be carried out: - if it is not based on the latest state of* ***scientific knowledge*** *and on a sufficient preclinical experiment; - if the* ***foreseeable risk*** *incurred by the persons lending themselves to research is out of proportion with the* ***benefit expected*** *of such persons or the interest of such research; - if it is not intended* ***to extend the scientific knowledge*** *of the human being and the means likely to improve his condition "and "****The interest of people who participate to research involving the human person always takes precedence over the interests of science and society alone****". "The search can only begin if all the conditions are met. Their respect must be constantly maintained."* article L.1121-2 CSP.

Unlike what is declared in Europe by some stakeholders, I don't think that EU Regulation as applied in France will provide benefits or advantages to patients.

The implementation of EU Regulation in France restrains the independence and the field of intervention of REC/CPP and does not follow the principles of the Helsinki Declaration neither international Good Clinical Practices GCP ICHE6.

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2 The impact of the new UE Regulation 536/2014 on the RECs of different European countries. Description, pros, cons, surfeits and deficits

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THE CURRENT SITUATION

Over the last five years, Italy has been involved in 17-18% of clinical trials with medicinal products for human use approved in the European Union. In 2015, 672 clinical trials were approved by the Italian Competent Authority (the Italian Medicine Agency - AIFA), 70% of which were multicentric and 24% were classified as "no profit"[1].

Unlike other Member States, all Italian Research Ethics Committees (RECs) are currently qualified to evaluate clinical trials with medicinal products falling under the European Regulation 536/2014. In addition, RECs are competent for clinical investigations with medical devices (pre- and post-market) and for observational studies with medicines. Also all studies involving other types of interventions, genetic studies and epidemiological observational studies (eg. registers) are submitted to the local REC, as the Italian Data Protection Authority has established the need of the local REC opinion for all studies involving the collection of data and/or biological samples. In some Regions, RECs also provide advice on ethical problems that arise in clinical practice.

To our knowledge, no national data on RECs overall activity is available: from a survey on a small sample of RECs, it can be estimated that clinical trials falling under EU Regulation 536/2014 represent from 30% to 65%. This figure needs to be taken into account in assessing the impact of the EU Regulation on the RECs activity and in planning their reorganization.

In Italy, the RECs number has been progressively reduced over time, from 304 in 2003 (one for each Local Health Authority) to the current 96. An important reorganization occurred in 2012, when a Legislative Decree[2] (then converted into a Law) established the population criterion of one REC per million inhabitants (with an exception for the big research hospitals, that can have their own REC).

At the same time, many Italian Local Health Authorities have been merged (eg in Tuscany, Veneto, Emilia-Romagna). This phenomenon has been called "merger mania"[3].

ONGOING CHANGES

Although Regulations are "directly applicable in all European Union countries"[4], actually in order to make the EU Regulation 536/2014 concretely enforceable, it will be necessary to amend the current Italian legal framework.

A Draft Law, already approved by the Senate, is currently under examination by the Chamber of Deputies[5]. It will give our Government the mandate to reform the current legislation on clinical trials.

Within 12 months of the entry into force of this law, the Government will have to approve the legislative decrees needed to co-ordinate the existing rules and EU Regulation 536/2014 "*in compliance with international standards for ethics in medical research on human beings and in accordance with the Helsinki Declaration of the World Medical Association of 1964, and its subsequent revisions*".

Some points of this Draft Law directly concern RECs, as it establishes that the subsequent legislative decrees will have to:

– Identify duties and objectives of local RECs.
– Foresee the suspension of the activities of RECs that do not comply with time limits and procedures set by the legislation.

Meanwhile, in December 2016, AIFA and the Ministry of Health have signed with the associations of pharmaceutical and medical device companies a "Memorandum of Understanding", called "Fast Track", which provides for a rapid authorization procedure for clinical trials on medicinal products and for clinical investigations on medical devices[6].

Accession to Fast Track by Regions, clinical trial sites and RECs is voluntary. The REC of the coordinating site (appointed to give the "single opinion") undertakes to express its opinion within 30 days of receipt of the application; RECs of the other sites involved in the trial should accept or refuse this single opinion within 20 days. General Managers of Local Health Authorities are required to accept a standard contract template and sign it within 3 days of the REC's opinion.

THE FUTURE OF RECS

Regulation 536/2014 provides that it should be left to the Member States to organize the involvement of RECs in the assessment, within the timelines of the authorization.

At the moment, no official declarations have been received by the Ministry of Health and the Italian Medicines Agency about the future arrangement of RECs in terms of number and responsibility.

In the summer of 2015, the then director of AIFA, Luca Pani, during an interview with a national newspaper, supported the need of a single national REC, arguing that this is dictated by the EU Regulation. This statement triggered an intense press debate, among local RECs supporters and those who demanded their abolition. It has, however, been noted by many authoritative voices that the Regulation provides for a single opinion at national level, not for a single national REC[7].

Someone pointed out that a national REC examining about 600-700 clinical trials a year (50-60 a month) would require its members a big commitment, hardly compatible with a full-time job, especially in case of clinicians.

The Italian Committee for Bioethics got involved in the debate with a motion supporting, among the various possible solutions, the establishment of a national REC, coordinating a limited number of local RECs. This RECs may have territorial competence or may be specialized in particular therapeutic areas. The national REC could directly evaluate some studies and entrust others to local RECs[8].

Although this would be an intermediate solution, which allows to "save both ways", it is unlikely to be practicable, given the strict timelines imposed by the new Regulation.

The most plausible hypothesis is that there will be a further REC reduction (perhaps to reach a REC for each Region) and the remaining ones will be in charge, in turn, to give the single opinion.

The reduction of local REC will be necessary also for economic reasons, because of the reduction of incomes from fees paid by sponsors. RECs unable to assure the required efficiency will likely not be selected to collaborate with Competent Authority in assessing the application, will see a reduction in their activity and consequently in their revenue and will no longer be economically viable.

Furthermore, as EU Regulation 536/2014 provides that "*Member States should not require multiple payments for different bodies involved in the assessment*", incomes from fees will have to be divided between Competent Authority and RECs.

In order to prevent this phenomenon, some Regions are already progressively reducing their RECs, even before national indications are approved.

It is important to remember that local RECs will continue to guarantee the evaluation of all studies that do not fall under EU Regulation 536/2014 and give advice on ethical problems in clinical practice. It is desirable that Regions will take into account all the activities carried out by the RECs, before reorganizing and merging them.

PROS OF THE EU REGULATION

The main purpose of the EU Regulation is to simplify and standardize procedures, in order to ensure timely approval of clinical trials on medicines and to make Europe more competitive in this field. Actually, it is likely that when the European portal will be fully implemented and the Regulation completely enforced, life of clinical trial sponsors will be easier!

Our Competent Authority declares that this will automatically result in an advantage for patients, as they will have an easier and faster access to innovative medicines. Actually, no one can guarantee that patients will benefit from a faster access to medicinal products that are, by definition, still under evaluation.

There will rather be a direct benefit for citizens and for national health systems if the simplification introduced by the EU Regulation will be exploit to conduct trials with public health objectives.

A positive element introduced by the EU Regulation is the opportunity of conducting trials in emergency situations, that was hindered in Directive 2001/20/CE by the impossibility for the subject to receive prior information and to provide prior informed consent. Nonetheless, this and other innovation will remain only a postulate, of no practical application, until the Italian legislative framework has changed.

CONS OF THE EU REGULATION

EU Regulation resumes the overcome separation between scientific and ethical issues. It foresees the possibility that RECs can be involved in the evaluation of Part II of the Assess-

ment report and excluded from Part I, which cover the assessment of the risks and benefits for the participants, the relevance of the experimentation and the methodological aspects (study design, sample size, statistical tests, etc.).

In Italy, it is very likely that the appointed REC will also be involved in the evaluation of some aspects of Part I, as this is what is happening for trials evaluated within the pilot project "VHP". However, as REC and Competent Authority assessments will partially overlap, it is unclear what will happen in case of disagreement.

With the new Regulation, the main requirement for a REC is to respect timelines and procedures: "*Member States shall ensure that the timelines and procedures for the review by the ethics committees are compatible with the timelines and procedures set out in this Regulation*" (article 4).

Efficiency is of course a positive feature, but it cannot be the only one and should not be the main one for committees appointed to ensure well-being and safety of people involved in research.

From this point of view, the EU Regulation and the Helsinki Declaration stand at a very different and perhaps irreconcilable levels[9].

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3 Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V. Germany

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The EU Clinical Trial Regulation 536/2014 (CTR) and its implementation in Germany lead to substantial changes of the established, well-accepted and effective system of reviewing clinical trial applications by Ethics Committees (EC), which impair their independence. For the first time the German federal legislator specified in detail the composition, functioning, tasks and responsibilities of ECs. ECs have to be registered with the federal drug authority BfArm, and in case an EC does not perform properly the registration can be withdrawn. In addition the drug authorities may override the negative opinion expressed by an EC. The ECs will lose their financial autonomy too as the fees will be fixed by the federal government. The tasks and responsibilities of the ECs remain almost entirely unchanged however. The ECs remain involved in the assessment of both parts of the application dossier: part I is assessed together with the drug authorities, the drug authorities having the lead. The assessment of part II remains in the sole competence of the EC. As the deadlines for the assessment became rather short, in particular for multinational trials, and the communication with the sponsor will be in writing only, the established procedures of ECs have to be modified. Up to now it was common to verbally discuss problematic issues with the sponsor. The CTR is focused on written communication with the sponsor via the EU portal. Ethics Committees, their office staff and chair persons will need considerable professionalism and respective training. The future workflow requires substantial IT support. The Ethics Committees and their Association of Medical Ethics Committees in Germany will do their utmost to protect efficiently the research subjects and to promote Germany as a major destination for clinical research.

The impact of the new EU Regulation 36/2014 on the RECs of different European countries. Description, pros, cons, surfeits and deficits. Current situation and perspectives in the Slovak Republic

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DEVELOPMENT AND PRESENT SYSTEM OF ETHICS COMMITTEES IN SLOVAKIA

In the Slovak Republic (Slovakia, SR), the present system of ethics committees to review both ethical problems stemming from the health care provision and from conducting biomedical research, including clinical trials of medicinal drugs, was gradually established since the year 1990, following and paralleling the unprecedented political, economical, social, and cultural changes that had been brought about by the so-called Velvet Revolution of November 1989 in then Czecho-Slovakia. These formidable developments were described in much detail in our previous publications[1-9]. The outline of the main milestones of those is given in the table 1.

The present system of ethics committees in Slovakia, which has stemmed from the above mentioned efforts, is characterized by[6,7]:

1. So far a *de-centralized ethics review* of clinical trials proposals seeking authorization by the National Institute for Drug Control (national medicinal drugs authority), albeit the so-called *single opinion* (according to the requirements of the EU Directive 2000/20/EC) valid for the whole country is issued by the so-called leading ("multicenter") Ethics Committee (chosen and approached with a written request by a sponsor), which is, on the other hand, done only after the Ethics Committees of all prospective institutions, where the clinical trial would take place, have been consulted by this "leading" Ethics Committee;
2. Existence of *combined Ethics Committees*, i.e. reviewing/giving their opinion both on ethical issues stemming from the health care provision ("clinical bioethics") and on ethical acceptability of the biomedical research proposals, including clinical trials of medicinal drugs for human use ("(clinical) research ethics");
3. Existence of the following *types of Ethics Committees*:
   – *Ethics Committee of the Ministry of Health* – it usually does *not* review research or clinical trials proposals, it rather functions as a "national bioethics committee", it could be consulted by other Ethics Committees, or even by other interested parties, in case of new or unusual or highly controversial ethics issues are encountered;

TABLE 1. Milestones of the Development of Ethics Committees in Slovakia: 1990-2017.

- 1990 - Central Ethics Committee (CEC) (= National Bioethics Committee) established at the Ministry of Health of the Slovak Republic (MH SR)
- 1991-1992 - ethics committees established in research institutions and major teaching / university hospitals in Slovakia
- 1991 - Chair of Medical Ethics at the Institute for Postgraduate Education and Training of Health Care Professionals (IPEHP) in Bratislava founded (postgraduate education, development of bioethics, publications, teaching activities, international conferences, etc.)
- 1992 - Institute of Medical Ethics and Bioethics (IMEB) established as a joint research and education facility of IPEHP and of the Medical Faculty of the Comenius University in Bratislava (undergraduate teaching - students of medicine, postgraduate education - health care professionals)
- 1992 - the first national *Guidelines on Establishment and Work of Ethics Committees* published by the MH SR (prepared by the CEC)
- 1993 - Institute of Medical Ethics and Bioethics Fdn. (IMEB Fdn.) established to support the works of IMEB
- 1994 - Journal "*Medical Ethics & Bioethics*" founded, its publishing supported by IMEB Fdn.
- 2002 - *Program of Revitalisation of the System of Ethics Committees in the Slovak Republic* prepared and gradually implemented by CEC
- 2002 - 1st National Meeting of Ethics Committees organised by IMEB Fdn. and CEC (in 2017 - 20th Meeting took place (on 20.4.2017)
- 2004 - *new Health Law* (576/2004 Coll.) – new provisions for local and regional ethics committees, and for CEC; it included several provisions dealing with bioethical problems (previously not explicitly covered)
- 2014 - initiative for preparation works on implementation of EU Reg. 536/2014
- 2014-2017 – work on implementation of the EU Reg. 536/2014 conducted (see the text for details)

– *Ethics Committees of the Upper-Tier Territorial Units* ("regional") – these review ethical problems stemming from the health care provision in their region (territory of the Slovak Republic in divided into 8 UTTUs), as well as evaluate and give opinion on ethical acceptability of the *outpatient* biomedical research proposals, including *outpatient* clinical trials of medicinal drugs for human use to be conducted in the region (UTTU); if chosen by a sponsor, this Ethics Committee gives a *single opinion* according to the requirements of EU Directive 2000/20/EC, however, only after the Ethics Committees of all prospective institutions, where the clinical trial would take place, have been consulted;
– *Ethics Committees of the Hospitals or of the Inpatient Research Institutes* ("local") – these review ethical problems stemming from the health care provision in their institution (hospital, inpatient health care/health research facility; there are about 70 such ethics committee in Slovakia at present), as well as evaluate and give opinion on ethical

TABLE 2. Education and Training Activities and Resources for Ethics Committees in Slovakia.

- Continuing, *devoted section* in the journal *Medicínska Etika & Bioetika – Medical Ethics & Bioethics* (the journal published since 1994 with support of the Institute of Medical Ethics and Bioethics Fdn./n. f.; the section since about 2004, with some letups)
- Continuing, *devoted section* at the *web page* of the Institute of Medical Ethics and Bioethics Fdn./n. f. in Bratislava (www.bioetika.sk/www.bioethics.sk) (since 2009)
- *Annual Meetings of Ethics Committees in Slovakia* (since 2002; in 2017 already 20th Annual Meeting took place) with educational, discussion, networking and experience sharing program
- *Postgraduate courses on medical ethics/bioethics* offered by the Institute of Health Care Ethics of the Slovak Medical University in Bratislava (since 2011, at least 2-3 different courses organised per semester)
- *Postgraduate courses on clinical trials methodology and Good Clinical Practice* offered by the Institute of Pharmacology, Clinical and Experimental Pharmacology of the Slovak Medical University in Bratislava (since 1992); state-accredited certification study program is also available (duration 1 year, state-guaranteed certificate id awarded)
- *National and International Bioethics Conferences* (co-)organised by the Institute of Medical Ethics and Bioethics Fdn./n. f. in Bratislava, or by other institutions/initiatives
- *Expert consultation support* given to Ethics Committees, their members and users, by staff of the Institute of Medical Ethics and Bioethics Fdn./n. f. in Bratislava (since its establishment in 1994) and of the Institute of Health Care Ethics of the Slovak Medical University in Bratislava (since 2011)

acceptability of the *inpatient* biomedical research proposals, including *inpatient* clinical trials of medicinal drugs for human use to be conducted in their institution; if chosen by a sponsor, an Ethics Committee gives a *single opinion* according to the requirements of EU Directive 2000/20/EC, however, only after the Ethics Committees of all prospective institutions, where the clinical trial would take place, have been consulted.

Since it establishment, a lot of efforts have been made to support country-wide networking, collaboration of Ethics Committees, as well as the education and training of their members. Most important existing education/training activities/resources for Ethics Committees in Slovakia at present are given in table 2. Having been represented by the Institute of Medical Ethics and Bioethics n. f. in Bratislava as a research partner (FP6 and FP7 Research Projects EUREC and EURECNET), Slovakia's Ethics Committees have also taken part in the activities of the *European Network of Research Ethics Committees* (EUREC).

IMPLEMENTATION OF THE REGULATION: THE MOST IMPORTANT ISSUES

The preparation work on implementation of the Regulation in Slovakia started soon after its passing by the European Parliament on April 16, 2014. Firstly, an informal, initiative work-

ing group was set up by the representatives of the Slovak Society of Clinical Pharmacology (branch of the Slovak Medical Association), the Slovak Medical University in Bratislava, the Association of Innovative Pharmaceutical Industry in Slovakia (AIFP), and the Association of Contract Research Organizations in Slovakia (SACROP). After some in depth study of the Regulation, the group evaluated then actual legal and 'real life' situation in Slovakia, and pinpointed the most important tasks to be accomplished and issues to be dealt with to achieve a successful Regulation's implementation. Later on (2015), an official working group, comprising all relevant stakeholders, has established at the MHSR. The Ministry also has overtaken the working group's management and provided a necessary professional support to its works by involvement of the respective Ministry's professional sections. As of writing this paper, the work has already reached quite an advanced stage in conceptual, preliminary designing the necessary legal, institutional, and procedural changes to be implemented by respective country's institutions and organizations to achieve successful implementation of the Regulation.

The said concrete, important issues being worked upon may be listed as follows:

- Changes (amendments) of the existing applicable Slovak Republic's legislation, especially the Laws No. 576/2004 (the "Law on Health Care") and 362/2011 Coll. (the "Law on Medicinal Drugs") (both as later amended);
- Structural changes and developments at the National Institute for Drug Control (NIDC) (acts as the National Competent Authority (NCA)), including hiring and specific training of about 30 professionals / experts, creating a devoted organizational section with an appropriate administrative and managerial support to organize and conduct scientific review of the clinical trials proposals both when Slovakia would be acting as a Reporting Member State or a Member State Concerned, as well as performing all other related necessary duties and tasks of NCA, including those of the "national contact point", under the Regulation;
- Establishing of the Ethics Committee of the Ministry of Health for the Clinical Trials (EC MHSR CT) to serve as a single Slovakia's Research Ethics Committee dealing with all clinical trials that are to be reviewed, approved, and further supervised according to the requirements and provisions of the Regulation; training of the EC MHSR CT's members and collaborating experts;
- Establishing of the "National Portal" to enable smooth and effective communication and management of the work of both NIDC (Slovakia's NCA) and of EC MHSR CT conducted by those bodies when fulfilling the tasks and requirements of the Regulation; the Portal is planned to include also functionalities for any necessary communications with "local" or "regional" Ethics Committees, as necessary;
- Dealing with the problems of funding of the whole said system to be put in place and sustained fully operational and upon the high level of trusted quality; this includes the problem that the fees paid by sponsors to NCA (just one fee to be paid according to the Regulation per a clinical trial proposal) would go directly into the State Budget, and would not stay, under current legal provisions, in the system, i.e. they are not available directly to provide for its necessary financial coverage; the problem is being dealt with at present within the negotiations between the MHSR and the Ministry of Finances SR (it is believed the chances for finding a workable solution are very good);

- Enhancing the competence and quality of the "local" and "regional" Ethics Committees to enable those to perform at an appropriate level of quality their tasks with regard to evaluation/providing opinion on the local/regional ethical aspects of the proposed biomedical research projects, including medicinal drugs clinical trials – if being asked to do so (e.g. within the feasibility study conducted by a monitor or CRO, or before signing a clinical trial agreement by a statutory organ (director) of a research institution (e.g. hospital, research institute) (mandatory under presently applicable biomedical research legislation in Slovakia – Law No. 576/2004 Coll., as later amended); and also performing their tasks with regard to ethics consultation, education, and building up an appropriate research institution's culture, enabling a genuine protection of research/clinical trials subjects' lives, health, well-being, and legitimate interests;
- Training of the "local" and "regional" Ethics Committees' members, as well as education and training of investigators, monitors, staff members of the Contract Research Organizations operating in Slovakia, health care organizations and research institutes managements, and other professionals taking part in clinical trials planning, authorization, conduct, and reporting; for Ethics Committees' members and investigators the requirement to pass a state accredited educational/training program will probably be made mandatory by the foreseen legislation amendments (obtaining certificate in clinical trials methodology and Good Clinical Practice).

THE SOLUTIONS UNDER PREPARATION – DECISION TAKEN

At present, the issues outlined in the previous paragraph are being worked upon by respective professional sections of MHSR, as well as by the various stakeholders involved, to achieve consensual, effective and efficacious solutions. The results of the work are being discussed within the informal ad hoc working groups, and directly among the members of the official all stakeholders' working group of MHSR. In reasonable intervals, the plenary meetings of the Ministerial working group are convened to evaluate the progress achieved, and to discuss outstanding items/issues, where consensus finding and mediation are still necessary.

The work, as outlined, has produced till nowadays already an advanced legislative proposal covering in almost already a consensual manner the necessary provisions to be incorporated into the Slovakia's applicable laws. The final, well prepared, and already broadly discussed law proposal should enter the legislative process in September or October 2017, so it would pass on time to enable having all necessary structures established in place, the new professional and expert workers properly educated and trained, and thus having the "national system" fully operational by September 2018.

For the purpose of the said legislative proposal the decision was made, after a thorough deliberation, that an option of having just a single Slovakia's Research Ethics Committee dealing with all clinical trials that are to be reviewed, approved, and further supervised according to the requirements and provisions of the Regulation [i.e. the said Ethics Committee of the Ministry of Health for the Clinical Trials (EC MHSR CT)] was clearly preferable, or even the only one actually feasible. Arguments for not using for this purpose the existing de-centralised

system of research ethics review already in place in Slovakia (as described above) were mostly pointing toward the feasibility of achieving professionally – ethically competent decisions on clinical trials proposals within the time frames/deadlines as required by the Regulation. At the same time, it was decided that existing system of Ethics Committees in Slovakia should not only be kept in place to enable fulfilling their irreplaceable tasks and roles with regard both to the clinical trials realm, and to biomedical research area, but that it should be further improved and adequately supported, to provide, among other issues, for an appropriate institutional ethical culture, education, consultation, and for a genuine research subjects' protection "at the ground level" (i.e. where the actual clinical research is being conducted).

On the other note, the "national portal" design and implementation has already been entrusted (after an appropriate selection procedure and by an official agreement signed by MHSR) to a reliable IT provider company. Progress of the works on the portal is regularly reviewed and details are discussed with the prospective users (esp. NIDC and EC MHSR CT).

Educational and training activities are being more actively offered to the Ethics Committees' members and users, as well as to the investigators. The necessary new personnel is being sought and hired as much as available both by NIDC and MHSR. There are some problems encountered, however, with regard to the new manpower availability, qualification, and motivation (including available, relatively low remuneration schemes that could be offered within the existing, rather modest state employees' remuneration system). Also, the system of funding of the necessary developments as described has still not been agreed.

SOME RISKS FORESEEN AND THE MEASURES OF THEIR MITIGATION

The major risk identified so far may be enumerated as follows:

- Risks related to the legislative process necessary to amend the applicable Slovakia's legislation in a full compatibility with the Regulation (i.e. successful passing of the rather complex law proposal mentioned above);
- Availability of the appropriately educated/trained personnel, hiring necessary number of new professional workers by MHSR and NIDC (NCA);
- Availability and motivation of external expert reviewers for both scientific and ethics review of the clinical trials proposals;
- Adequate availability of funding to cover the necessary system development and operation;
- Failure of the relevant Government officials/departments to acknowledge and support the necessity of a successful implementation of the Regulation in Slovakia as a genuine priority.

The above mentioned risks are not all deemed trivial, or merely hypothetical. Therefore, a devoted information and education work is being done at present by various stakeholders involved. It is directed, first of all, toward the relevant structures of MHSR, and other Ministries. No less important, however, are deemed to be the information and education activities aimed at the professional and the general public, with a special attention being given to the patients' organizations and patients' representatives [e.g. also within the activities of the Slovak Chapter of the EU Project EUPATI (stands for the European Patients' Academy

for Therapeutic Innovation), which was successfully established in 2016]. It is hoped these activities will ensure necessary understanding and public support for the planned complex and quite demanding legal, institutional, and procedural changes.

CONCLUSIONS

An outline of the EU Clinical Trials Regulation's implementation work, which is being done in Slovakia in collaboration and coordination by the relevant stakeholders involved, allows to conclude that Slovakia's efforts in this area are well posed to be successful and in keeping with given time frameworks. A lot has to be done, however, to achieve the desired outcomes and deal with inherent risks and rather complex problems encountered in this dynamic and rather complicated area.

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5 EUROPEAN Research Ethics Committees: "What kind of REC can fit Europe?"

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INTRODUCTION

The original reason for creating Research Ethics Committees (RECs) was to ensure respect for participating subjects, avoiding their instrumentalisation in the name of knowledge or science. It was, essentially, an ethical concern: knowledge and science are not absolute moral criteria. In the words of Kant ("Grounding for the Metaphysics of Morals", 1785): "Act in such a way that you treat humanity, whether in your own person or in the person of any other, never merely as a means to an end, but always at the same time as an end."

It is not easy to be a good Research Ethics Committee (REC). Evaluation, monitoring and support are the basic "REC functions". However, although they are basic functions, how they are done is crucial. A REC must be independent in evaluation, responsible when monitoring, rigorous and efficient with procedures, deliberative in ethics, interactive in support and representative of society and research community, and not slow without justification.

RECs have a double commitment: to ensure protection and promotion of people's rights, avoiding exploitation and discrimination, and to the quality of the research that produces knowledge and improves citizens' well-being. Therefore, who decides: committees or citizens? The important debate must take place within society, with total transparency. Sensitisation to the possible good and bad effects of research is a key element. Citizens must set goals and research priorities, that is, determine the pertinent questions to answer, which principles and limits are essential and which procedures we need to follow to finally reach solid ethical, methodological and social evaluation leading to good trials and projects.

The Declaration of Helsinki[1] is one of the fundamental texts on ethics in research. In point 23, it says: "The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence, and must be duly qualified. As such, RECs have been, and still are, key elements in the assessment of research projects all over the world, and not only for clinical trials. They are ethics committees, but they also have "executive" functions, approving, changing or rejecting each project with a public judgement. In most European countries, it is illegal to start a research project without this approval.

In addition, research ethics committees must go beyond the documents (protocol, informed-consent forms, etc.), to evaluate real acts in research and promote good practice. They also carry out important monitoring functions, as well as relevant teaching and guiding roles, through interaction with clinicians, researchers and citizens.

THE DUAL NATURE OF RECS

Research Ethics Committees have a dual nature. They are evaluation structures, but also deliberative teams. The Spanish Royal Decree 1090/2015[2] defines RECs as "independent and multidisciplinary bodies set up to ensure the protection of rights, safety and welfare of people involved in a biomedical research project, and also provide a public guarantee for this project, passing a judgement on the project documents, taking into account the views of lay people, in particular patients or patients' organisations".

It is important to note that the words "corresponding to the research centre" don't appear in this definition, despite being present in the Biomedical Research Law (14/2007)[3]. This may seem to be an insignificant detail, but perhaps reveals some strategic aims associated with the new evaluation model. This model changes significantly if, in practice, RECs are not necessarily ascribed, or "related", to one or more research centres. Law 14/2007 states, in article 12, that Research Ethics Committees "corresponding to the centres conducting biomedical research must be duly accredited by the competent body [...] to ensure their independence and impartiality".

What is the relationship between ethics, RECs and the law?

Any new legal text must be inspired by ethical reflection, without coercion, and always detecting potential conflicts of interest. The Declaration of Helsinki already emphasises the duty to respect research-related laws but as long as these do not weaken or eliminate any of the protections that the same declaration establishes for people involved. Throughout history, some tense balance between ethics and the "establishment" has always been present in the social framework.

Regulations must become an instrument, not a cage, for ethical deliberation. On the other hand, bioethics is increasingly important in a context of research with high levels of "technification" and diversity, and under pressure from "market laws"[4]. RECs are key players in the search for balance between "research freedom" (to achieve scientific and technical progress), social progress, and people's rights (people participating as "research subjects" or yielding their personal data or biological samples).

Research as an important economic sector

At the moment, research, like healthcare, is a dynamic economic sector (investments, patents, complementary services, etc.). The confluence of competitive, transnational and multicultural interests (the "biomedical market") makes it difficult to identify and preserve the ethical dimension of RECs' mission. Knowledge and treatment of illness are no longer the only motivations behind research.

Symbolising this, international "Contract Research Organisations" are proliferating, piloting trials all over the world in the name of efficiency, and assuming many of the promoters'

tasks. This reduces initiative and, indeed, the involvement of the researchers themselves in research leadership. This conflict of interest between industry and citizens persists in the background of clinical trials, especially those driven by pharmaceutical companies' commercial interests. The new model conditions the leadership of researchers in research and disconnects the real interests of society from the "research questions". Could research in humans become solely an economic matter; an "investment machine"?

The European context

In Europe, during recent decades, there has been a progressive loss of "competitiveness" at a European Union level (although not in Spain) in relation to the attraction of clinical trials. Consequently, there is a gradual switch to Eastern European or other developing countries[5]. This is thought to be due to the bureaucratic rigidity of our norms, and the assessment schedules of European RECs.

It was thought that a new European Regulation[6] (ER 536/2014, European Parliament and Council), which repealed European Directive 2001/20/EC[7], would make the normative interpretation of the various Member States less flexible, thus promoting international clinical trials. The European Regulation does not specify how to guarantee that ethical reflection is included in the global assessment process, preserving the autonomy of each state in defining evaluation procedures and REC regulation.

However, RECs must not become silent witnesses to innovation and development processes without any capacity to modify or improve them. This is very far from their original aims. On the other hand, research institutions have to maintain some ability to control and audit their research process.

THE "REC DENSITY DILEMMA"

Another dimension of the current dilemmas related to the future of ethical evaluation of research projects is the right "density" of committees by country or region, or by trial. The current trend is to centralise evaluations in the name of efficiency and speed, with the aim of promoting clinical trials in the European Union.

The REC landscape in Spain, prior the most recent royal decree

In 2013, there were 136 accredited RECs in Spain for a moderate level of research activity (0.95/1,000 citizens). Only Belgium (264) and Italy (215) had a greater density of RECs but these countries carry out more research activity (1.13/1,000 & 1.5/1,000 citizens, respectively)[8].

In 2015, RECs in Catalonia and Madrid evaluated 79.1% of trials in Spain. Catalonia had 32 RECs, but only 16 have ever acted like "reference REC" in the evaluation of clinical trials. Concentration of assessments is clearly not a recent phenomenon.

Beyond this, around 50% of projects assessed in Catalonia are not clinical trials, and these kinds of projects increasingly need careful ethical and technical assessment due to the rapid growth of new research areas (genetics, big data, nanotechnology, complex devices, bioinformatics, etc.).

Legal changes are already here

On Christmas Eve 2015, racing to pass the legislation before the holidays, Spain was one the fastest states to adapt law to ER 536/2014, with previously-mentioned Royal Decree 1090/2015 also regulating RECs for clinical pharmacologic trials.

Other countries have already adapted their laws (Portugal, Denmark), with similar consequences; reduction in the number of RECs and concentration of assessments, strengthening of links within RECs and State Regulatory Agencies and disaggregation of clinical trials with medications from other kinds of research projects.

Thus, the new text outlines a new legal framework for clinical trials in Spain, with increasing requirements for RECs in accreditation and operation. Not all RECs will be able to evaluate clinical trials with medicines, creating a new kind of specialised REC, the "RECm". Only this kind of accredited REC will be able to evaluate these trials. Existing RECs have until January 2018 to obtain this accreditation.

Only a single "Spanish opinion", only one REC per trial

Only one REC in Spain will evaluate each clinical trial, and this REC will be selected by the promoter. The new decree encouraged a centralised evaluation model, removing the previous mandatory intervention of all local Ethics Committees. In the end, for clinical trials, the local REC role disappears, establishing a single "Spanish opinion". The opinion of the selected REC will be considered binding for all centres. That is, trial approval will depend on the state agency (AEMPS) and the sole REC (chosen by the promoter). For this reason, a single rate per evaluation will be charged by State Regulatory Agency (AEMPS), which will then deliver part to the evaluator REC.

Suitability of facilities and researchers. Monitoring tasks

Without proper facilities and good researchers, any project loses its purpose, generates more risk and produces less knowledge. However, taking every possible precaution during the preliminary assessment makes no sense if there is no proper monitoring of the study by the responsible REC, a tool that ensures that scientific spirit and respect for bioethical principles remain intact within the research team. Monitoring and auditing are very important for what looks good on paper; this will also be the case in practice.

Even with the previous "proximity model", it was already difficult for closer committees to be certain that things were going well in the development of supervised trials. They were concerned, in many cases, about an inability to carry out this task with enough rigour.

In the new scenario, the REC responsible for monitoring a trial can be located far from the research centre, researchers and participants, limiting its capacity to carry out rigorous evaluation of facilities and appropriate project monitoring.

Is a single REC per trial really appropriate for Spain...or for Europe?

If having only a single assessment REC means eliminating deliberation on the trial, the final report will not be an ethical evaluation. Perhaps we can debate how many RECs are necessary, of course, but one only REC per trial is probably not the best solution.

Simplification of evaluations is proposed with the aim of improving procedural efficiency but if that implies a weakening of the deliberation process, we will achieve no more than a

purely technical or administrative evaluation. The participation of RECs close to research centres is difficult to replace.

On the other hand, local differences such as the burden experienced by participants, cultural aspects, informed consent, etc. can be extremely important. Often, they directly affect people involved. With more observers and greater proximity, it is easier to identify risks and inconsistencies associated with these issues. That is, local aspects are not trivial, and centralised evaluation can lead to suboptimal supervision of these aspects.

Other REC tasks in the "real world"

It is also very important that RECs have a real impact on the field of research activity (training, debate, sensitisation, teaching, etc.). Respectful and communicative interaction with research professionals and others involved will make REC functions a valuable tool, rather than a purely bureaucratic procedure.

This can also help to ensure that the ethical aspects of research do not depend solely on REC members but become a focus of interest and responsibility for all players. To achieve this, RECs should involve, train and listen to citizens, researchers, monitors, managers and promoters.

But, what are centre managers really doing?

With the new model, managers can have trials taking place in their centre that have been approved by a single REC 1,000 km away, and these trials may be unknown to their "own" local committee.

Management always has the option of not allowing the trial to be carried out at its centre by refusing to sign the contract. In practice, they are asking for counselling of their "own" REC prior to providing the signature. And these RECs are currently "evaluating" trials without access all the necessary documents, without any regulatory support, and with the formal opposition of the Administration.

THE "DEPENDENCE DILEMMA"

Absolute independence, included in the RECs' original definitions and concepts, is hard to achieve for several reasons (managerial, financial, promotional, etc.). Closer RECs must be biased towards the interests of researchers and centres. A centralised REC could be subject to pressure from the administration and promoters, especially if they are selected by promoters. What is the "least bad" situation? Which bias can be compensated for more easily?

Should "evaluated" choose "evaluator"?

The selection of evaluator REC by the promoter (arbitrary and perhaps unnecessary), represents the strongest challenge to independence. This privilege of promoters was already present in the previous royal decree (RD 223/2004), but balanced by the required choral evaluation of all participating committees. In the new scenario, we have only one decision-making committee and, therefore, the impact of the selection procedure further

threatens the essential independence of any evaluator. As it stands, local RECs cannot access the trial information to evaluate it. The role of the local committee in clinical trials disappears with the current decree.

No doubt proximity to researchers and centres, as is the case with the previous model, can also introduce some evaluation bias. It is conceivable that known professionals evaluating projects could introduce a bias in favour of approval. From this point of view, a remote committee would be more objective. But, again, the obligatory choral evaluation of all local RECs reduces the consequences of this potential bias.

We have already remarked that breaking the link between evaluator REC and researcher can produce "side-effects" and compromise monitoring, evaluation of facilities, supervision of the informed-consent process, and so on. In conclusion, the selection of the REC by the promoter is a high ethical-risk factor, especially if choral ethical evaluation is eliminated.

Economic viability and REC independence

As mentioned above, in Spain, the state regulatory agency will receive payment from the promoter and only one REC will receive part of the total amount. If, as to date, the logistic viability of committees depends on assessment fees, only committees chosen by the promoters will have a regular influx of economic resources. This scenario can generate a clear conflict of interest. Maybe promoters will prefer a quick committee, asking for little clarification.

This economic dependence cannot become a reason to relax evaluations. The REC must not become a kind of advisor to the state regulatory agency. Nevertheless, for clinical trials, the new Spanish regulation switches the link to centres and investigators for a link to the administration and promoters.

The word "supervision" often appears in this legal text and in the cooperation "memorandum" between the state agency and RECs. It is necessary to define this relationship (cooperation versus supervision) well in practice to preserve RECs' independence.

As mentioned above, the organisation of RECs in each state is open. Multiple interpretations are possible but, at the moment, all new legal adaptations in member states show a reduction in the number of RECs and a greater concentration of evaluations. Therefore, the deliberative "ethical core" of RECs' mission is at risk, especially if local committees tend to disappear, whether through administrative decisions or loss of financial viability.

For once, why not an "American way"?

The United States rule covering ethics in research with humans ("Common Rule") shows more procedural flexibility and maintains the proximity of committees to centres and researchers, and this framework does not seem to hinder strong research activity in the U.S.

We missed a discussion on this topic prior to the formulation of the new European Regulation: which would be better, centralised or local committees? And there should be an assessment of whether there has been adequate analysis of the situation surrounding clinical trials in Europe, and its power "to attract" trials. The possible lower cost of research in other countries (remuneration to volunteers, researchers and institutions, exams, complementary services, etc.) has had a greater effect than the evaluation and approval procedures. And it is difficult to dispel doubts on whether "flexibility" is perhaps more than "flexibility" in some countries.

TABLE 1.

	Near and many Centres linked	Far and Few State agency linked
Link	Centres	State agency
Bias	Researchers / Centres / Knowledge	Promoters / Government
Focus	Science / Prestige	Incomes / Investments / Business / Tax
Deliberation	++	+/-
Interaction	+++	-
Influence in "real world"	+++	-
Monitoring	+	-
Facilities & Researchers	+++	+/-
Quickness	+/-	+?
Expertise	+/- (they need counselling)	+ (in theory, easy access to experts)

At this point it should be clarified that, so far, the new regulations in Spain have meant a saving of about 2 weeks in the evaluation process by the research ethics committees. We should reflect on whether 2 weeks are really so damaging to a drug development process that often lasts over 15 years.

We can summarise the pros and cons of the two possible REC models in this table:

THE "COMPOSITION DILEMMA"

Who need RECs, "experts and specialists" or "ordinary people" with a bioethical approach and access to good basic training and counselling in the different areas relevant to research projects? Lay people improve the representativeness of the committee and experts offer knowledge about technical and scientific issues. Possibly a prudent balance of both contributions is recommended.

European Regulation (EU) 536/2014 refers to a REC thus: *"...a reasonable number of persons who collectively have the necessary qualifications and experience..."* and adds: *"...should be independent of the sponsor, the clinical trial site, and the investigators involved, as well as free from any other undue influence"*. Article 2, point 11 defines the 'Ethics committee' as an independent body empowered to give opinions for the purposes of this Regulation, taking into account the views of laypeople.

Therefore, competency is another essential requirement of regulations and international declarations for RECs. But does this mean that RECs must become "expert teams"? Clinical trials coexist with projects on regenerative medicine, cell or gene therapy, social interven-

tions, psychological therapies, educational programmes, surveys, scale validation, projects with modified organisms, bioinformatics, big data, health apps, etc.

Furthermore, investigation in vulnerable groups or with orphan drugs is fortunately increasing, creating new ethical concerns and challenges. We also have an increasing affluence of projects without the direct, physical participation of human beings in, for instance, projects based on biological samples or health data. Of course, it is important to be qualified in these different subjects but also in ethical deliberation.

RECs are advocates of society. If we create expert and specialised committees, will they be good representatives of "ordinary" or "lay" people? We need a balance between technical, scientific, legal or ethical competency and representativeness. It is difficult to find a team of people who are experts on everything relevant to research, because research fields are increasingly complex and diversified. Therefore, we propose to improve REC skills, tools and knowledge, ensuring rapid and efficient access to information and ad-hoc expert advice when necessary, but preserving a critical number of "ordinary people".

REAL CHALLENGES OF NEW RULES AND TIMES

In conclusion, what are the real challenges of the new framework?

Independence

The most important challenge is to preserve and maintain the independence of committees so that they can conduct evaluations free of conflicts of interest.

It is vital to carry out a dynamic evaluation compatible with the essential bioethical deliberation. As such, in our opinion, it is urgent to reconsider the legal precept that gives the promoter the power to choose the evaluator REC (only 1 in Spain). This, combined with the elimination of the requirement for choral evaluation, severely threatens committees' independence.

Of course, it is important to establish a cooperative relationship between RECs and Regulatory Agencies, avoiding functional dependence, taking advantage of synergies to improve evaluation procedures but without detracting from the essential mission of RECs or their independence.

Quality, transparency, accountability

The bureaucratic load is high for RECs. Especially in the new procedural framework, it is a challenge to organise Technical Secretaries to establish pre-reviews (documents, procedures, bureaucratic issues, etc.), ensuring members' access to all the essential elements for a good evaluation. Face-to-face meetings could be devoted to true bioethical deliberation, including of course methodological and social concerns.

Furthermore, REC accountability is required. RECs must also design good, transparent indicators of their tasks, including ethical evaluation. Similarly, RECs need a "check-list" of essential ethical issues to evaluate and consider. This "check-list" helps to structure reflection but it is not the reflection itself. Ethics needs time for dedication and for deliberation.

Ethics and time

Deliberation takes time, needs time. If this deliberation is to be choral, coordination takes time. It is also important to preserve public debate time during the approval procedures. Sometimes, after a meeting, some relevant concerns emerge. Rethinking is vital in ethics. However, time has limits in research, of course, even taking considerations of justice into account. Spending too much time on ensuring proper ethical reflection is also bad. It is necessary to find the optimal balance between "operative paralysis" and the total lack of rigour in evaluations.

FINAL THOUGHTS

We finish with some final thoughts and proposals for the "European REC":

- Ethics in research is a choral matter, systematic and dynamic (due to our social commitment), but choral and deliberative.
- Possibly we should rethink how many RECs per trial are necessary (their distribution is also important). Perhaps the correct answer is "not many", but never only one and far from "research acts" and "research people".
- A REC is not only an evaluation agency; it is an essential part of the research process.
- REC members are possibly "special citizens" but they must never forget that they represent citizens.
- Members' "over expertise" is perhaps a drawback. REC members need good advice, teaching and training, but perhaps it is not a good idea that only "experts" make decisions about the ideas and proposals of other "experts" that can affect "ordinary people". We need non-expert people in RECs, with proper support and information.
- Reduced workgroups and ad-hoc experts are, of course, useful in preparing projects for ethical deliberation but they cannot replace deliberation with diverse views and approaches.
- And, finally, RECs cannot evaluate, respect and protect without independence (psychological, hierarchical, financial, etc.). Evaluated should not choose evaluator.
- Ethics should not paralyse research without justification, but markets must not smash ethics..., and true research.

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6 KIDS Barcelona: The first YPAG in Spain

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The Clinical Trials Office (CTO) of Sant Joan de Déu Children's Hospital offers a research support to assist sponsors and researchers to perform clinical studies and is operated by Fundació Sant Joan de Déu. The CTO provides the scientific tools and facilities to execute, coordinate and/or facilitate paediatric clinical research studies, in a "one-stop/full service" model, facilitating this single contact point for external and internal sponsors, supporting the performance of commercial and non-commercial clinical trials.

The CTO has established a Young Persons' Advisory Group (YPAG): KIDS Barcelona. The YPAG works together with the Innovation Department with the goal to include the voice of children and families in research, clinical trials and innovation projects (Fig. 1).

Sant Joan de Déu Children's Hospital is the only paediatric hospital in Spain that has an YPAG. The team was created on 2015 and during this period has executed different activities:

- *Guidelines for the format and content of the assent document for clinical trials.* These recommendations have the aim to include the features of the paediatric population in the design process of this legal document. Ethics Committee of Fundació Sant Joan de Déu approvd the document in a monographic session with the participation of the members of Kids Barcelona. Afterwards, the Spanish Medicines Agency has approved the content

FIGURE 1.

FIGURE 2.

FIGURE 3.

of these guidelines and recommends their consideration to all the sponsors that perform paediatric clinical trials in Spain (Fig. 2).

- *Comic* to explain the 8 main concerns that children between 12 and 18 years old can have about clinical trials. KIDS Barcelona chose the topics and worked to develop an story suitable to be understood by children of their same age and to clarify with an easy language important information, such as: what is a clinical trial, the rights of the children, the assent document, etc. (Fig. 3).
- **Website** to educate and spread the word about the activities of the group: www.kids-barcelona.org The site offers information for children (8-12 years old / 12-18 years old) and for parents. At the same time is resource to disseminate among schools and to the general society about the need to increase the research in the paediatric drug development and the specifities of this research field (Fig. 4).

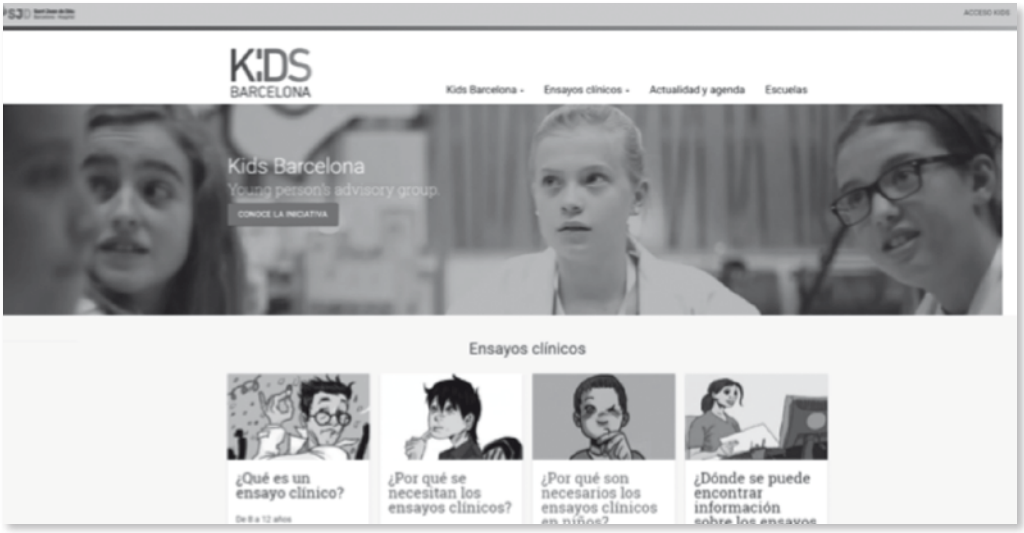

FIGURE 4.

FIGURE 5.

- Interactive tool to explain and educate about the process to develop a new drug. With this adventure children older than 11 years old can understand the goals of the different phases, what happens when a drug is not working and other content. The tool has been organized in different chapters that are the different phases of a clinical trial. When the explanation has been offered the users have to do an activity to demostrate that they have understood the information and they can go ahead to the next phase of the tool. The script of the story, the cartoons and the activities have been designed by Kids Barcelona. The tool is available in the website to be download (Fig. 5).

FIGURE 6.

- *ICAN Summit 2016*. KIDS Barcelona is a member of the umbrella organization ICAN (International Children Advisory Network) formed by all the YPAG that nowadays exist around the world. Last year our organization had the pleasure to organize the ICAN Summit focused in the whole concept of health: prevention and treatment. Regulators, pharma companies, researchers among other experts participated in the activities developed during a 5 days (Fig. 6).
- **eYPAGnet (European Young Persons' Advisory Group Network)**. Kids Barcelona is leading for the next three years this network. eYPAGnet has the recognition of EnprEMA (European Network of Paediatric Research of EMA) and is formed by 9 teams from UK, France and Spain. The main goals of the network are:
  - Improve the capacity to collaborate with the different stakholders involved in the process of research and development of innovative drugs: academia, regulators, ethics committees, pharma companies, etc.
  - To accumulate experience in relation with therapies for children and moreover in the most innovative treatments.
  - Promote the design and development of clinical research initiatives in children at European level.
  - Unify the curriculum for training programs and empowerment of young, expert patients.
  - Promote and lead the creation of new groups.

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7 Pragmatic ethical aspects for pediatric clinical trials

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INTRODUCTION

The objective of the Paediatric Regulation (Regulation EC No 1901/2006[1]) is to foster high-quality ethical research in order to increase the availability of safe and effective medicinal products authorised for use in the paediatric population. To meet this objective, the European Medicines Agency (EMA) established Enpr-EMA, The European Network of Paediatric Research at the European Medicines Agency, in March 2011 (Article 44)[(1)].

EnprEMA has formed several ad hoc Working Groups (WG) tasked with most important pragmatic needs related to making the most of paediatric research networks, and using networks to enhance paediatric Clinical Trials (CTs) and develop medicines for children. FinPedMed, a Finnish national network and a member of the Enpr-EMA, has developed various materials and a tailored training program to support the high ethical aspects of the paediatric CTs. Materials are designed for investigators, and in addition to companies designing and conducting the paediatric CTs.

In the near future, the development of electronic services, operations and electronic documentation will be daily routines in all sectors of life – also for CTs. For that, we will need advice also from the children and young people, as experts, to develop the most feasible patient information formats, informed consents (ICs) / assents and other trial documentation, to ensure high quality and secure medical research environment.

THE ENPR-EMA

Enpr-EMA is a network of research networks (national, age specific, disease specific, therapeutic area and knowledge specific), investigators and centres with recognised expertise in performing CTs in children[(2)]. Enpr-EMA's members are required to fulfil certain criteria for the membership. The operational centre of Enpr-EMA is the Coordinating Group (CG), which is responsible for the network's long- and short-term strategy.

The EMA provides the secretariat support to the various activities, such as the meetings of the network, ensuring the exchange of information between the network partners and stakeholders. Enpr-EMA works by allowing networking and collaboration with members from

within and outside the European Union (EU), including academia and the pharmaceutical industry. Enpr-EMA does not perform CTs or fund studies, or research, or decide on areas for paediatric research, as this is the responsibility of Member States, the European Commission or each individual member organisation.

ENPR-EMA ETHICS WORKING GROUP (WG4) & DELIVERABLES

In 2013, EnprEMA agreed to set up several ad hoc Working Groups (WG) tasked with addressing the most important of the needs related to making the most of the paediatric research networks. The purpose of the WGs is to develop pragmatic responses to meet these needs, implementable within six months. EnprEMA focuses on disseminating these existing good practices and new ideas across the stakeholder groups.

Paediatric CTs are often conducted as multinational trials. Informed consent (IC) or assent is part of the Ethics Committee (EC) approval for clinical trials. The consent requirements vary between countries due to national laws and regulations, which are not harmonized in Europe. These discrepancies can present challenges for paediatric CTs.

The Enpr-EMA Working Group 4 (WG4) focuses particularly on these ethical issues, and operates under the title "Dialogue and Interaction with Ethics Committees". The WG4 consists of experts and professionals, specified to work in the area of peadiatric CTs representing various stakeholders of the academia and the industry. The WG4 has been working since August 2013 and has produced several deliverables based on the identified specific ethical issues of pediatric CTs in Europe. First report in 2013, addressed to the Enpr-EMA CG, and included 12 different recommendations of short- and long-term tasks and possible deliverables.

THE "TOOL KIT" – A TABLE OF EUROPEAN REQUIREMENTS FOR IC AND ASSENTS

Afterwards, two years of planning, meetings and material collection, the working group published first deliverable; a "Tool Kit" - *Informed Consent and Assent for Paediatric Clinical Trials in Europe.* This "Tool Kit" is a table including 27 national IC and assent requirements listed by individual country (25 European Union Member States and 2 European Free Trade Association countries) and it was published on Enpr-EMA website on 18 December 2015, and has been updated by the Enpr-EMA secretariat since. After the completion of the Tool Kit, the related article: "*Informed Consent and Assent Tool Kit for Paediatric Clinical Trials in Europe*" was published on 25 May 2016[3].

In EEA countries, 18 years is generally the legal age for independent consent – some exceptions exists; 14 years in Austria, 15 years in Finland and Denmark, and 16 years in the UK. Additionally, there are 32 different age groupings (0-18 years) for consent / assent requirements, and three (3) countries (Croatia, Lithuania and Slovakia) do not have specific age groups for consent / assent. In Europe, there are also different definitions for legal consent and the requirement of legal signatures country by country and these criteria are not uniformly defined in European guidelines or recommendations for unknown reasons. The Tool Kit collates this data and it is publicly available for all those involved in paediatric CTs and

ECs, providing a new platform for proactive feedback on IC requirements. Finally, this may lead to a needed harmonisation process and uniform standards accepted across Europe[4].

SUGGESTIONS AND IDEAS TO SOLVE CURRENT IC / ASSENT PROBLEMS

The current wide variation in paediatric consents and assents presents challenges for multinational paediatric trials in Europe. To solve these identified IC / assent problems in Europe, authors suggest the measures and further development for uniform, commonly accepted standards and guidance across Europe and some definitions of the lowest age limit to consent and assent requiring child´s own signatures (in addition to parental, legal consent) until the legal age of majority permits independent consent. More importantly, the authors would like to start fundamental discussion, in order to create detailed general definitions for assent and IC documents, and to decide whether these terms could be harmonized. Standardized IC structure and reading level requirements of IC and assent documents, including recommendations for the legal guardian´s signatures, would present helpful guidance for all stakeholders. Finally, a master IC / assent template in all national languages being publicly and readily available, would offer more detailed suggestion about the necessary contents of these documents. This is the next task tackled by the WG4.

RESPONSE TO PUBLIC CONSULTATION OF THE "PAEDIATRIC ETHICS GUIDELINE"

One of the central ethical guidelines supporting for paediatric clinical trials in Europe has been the "Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors" ("Paediatric Ethics Guideline") originally published by EU Commission´s Ad Hoc group in 2008[5]. Due to the new EU Clinical Trials Regulation 2014 (CTR), the ethical processes for a new Clinical Trial Application (CTA) in Europe will face major changes[6]. The CTR will harmonize the CTA process, but IC / assent issues remain with each Member State. While the CTR is still waiting to be fully implemented in Europe (during 2018), the original "Paediatric Ethics Guideline" needs to be revised according to the CTR, being crucial to its implementation and achieving the CTRs' aims, and facilitating CTs of children and adolescents.

Second actual deliverable of the WG4 was a response to the EU Commission Public Consultation of the "Paediatric Ethics Guideline". The consultation represented the response from Enpr-EMA, its working groups (including representatives of networks, National Competent Authorities and pharmaceutical industry), and partners, and was contributed by European Forum for Good Clinical Practice, Children's Medicines Working Party (EFGCP CMWP[7]) in collaboration with a small group of EMA Pediatric Committee (PDCO[8]) members. The Revision document was submitted on 30 August 2016. The revision included extensive changes and many proposals for a new structure, as the original version was seen too complicated, lengthy and not very user friendly.

Some of the WG4 members contributed additional Enpr-EMA activities in 2016, such as contribution to PROPOSED CHANGES TO THE U.S. COMMON RULE - Implications for

Pediatric Research (Federal Policy for the Protection of Human Subjects). Comments to this document were submitted on January 2016.

"PARTLY HARMONIZED IC / ASSENT TEMPLATE -DOCUMENT" FOR PAEDIATRIC CTS

The latest deliverable of the WG4 is about "Partly harmonized Informed Consent / Assent template -document" for paediatric CTs. This work was prepared by a smaller Consent Group of WG4 during the year 2016, and it was finalized by the whole WG4 in March 2017. The document template format is based on the identification of all similar elements across the ICs and assents of the existing and publicly available templates (see: Tool Kit data and links to these documents). First version of this generalized template will be published on Enpr-EMA Annual Workshop on 16 May 2017, and afterwards the template will be made publicly available on Enpr-EMA website to be used for all stakeholders.

FINPEDMED & INVENTIONS TO SUPPORT HIGH ETHICAL STANDARDS OF PAEDIATRIC CTS

FinPedMed (Finnish Investigators Network for Pediatric Medicines), established in 2007, is a non-juridical joint venture of all (5) Finnish university hospitals which operates on an open, non-profit service concept basis to promote both academic and sponsored research in Finland[9]. The operational model of the network is based on its own (closed) membership register that enables it to quickly identify and offer experts and investigators for any newly opening expert positions and paediatric CTs. Currently.

FinPedMed has more than 160 registered members. Finpedmed´s legal Host Organization is Helsinki University Central Hospital (HUCH), Department of Children and Adolescents. The network is funded by the University Hospitals and it has been a member of the Enpr-EMA since 2011. While the average annual number of new paediatric CTs started every year in Europe is 460, the corresponding number in Finland is 24, representing 5% of the European paediatric CTs. For ECs and investigators, the FinPedMed network has produced patient information- and IC templates for all age groups, Picture Cards and several guidelines regarding paediatric CTs.

FINPEDMED PICTURE CARDS

During the year 2008, a group of experts stated that the use of illustrative material to aid the understanding patient information has thus far been minimal, and formed a picture card team to create a set of picture cards to be used by investigators to help paediatric trial participants understand the content of patient information. Knowledge of both developmental- and educational psychology, as well as neuropsychology was used in the planning of the cards. The content for the pictures was collected from literary, photographing at the

hospital's (HUCH) paediatric clinic, and by consulting experts and investigators specialised in paediatric clinical trials. Children, ages 1 to 6, attending a day nursery in Espoo commented on the coloured picture cards. The children were shown the cards in nearly all groups of all ages during their free time, and they could freely express what came to their minds, and day nursery staff recorded the anonymous comments on the pictures. Based on these comments the pictures were modified to better suit the objects and situations in question.

As a result, FinPedMed Picture Cards were produced in printed form inside a folder, including a set of 31 pictures of both objects and situations (i.e. different drug formulation and administration methods, basic medical examination situations, different additional examinations and procedures, pictures depicting time, visits to the hospital, the hospital environment and trial documents). All Picture Cards are labelled in Finnish, Swedish and English. The folder includes also a transparent No-card with a red cross. Picture Cards are usable by all professionals in clinical work with children and families[10].

FINPEDMED IC TEMPLATES FOR ALL AGE GROUPS

In 2009, a group of experts compiled by FinPedMed, designed IC documents and trial information sheets for children (under the age of 18) and their guardians to be used in clinical trials. All document templates are available also in Finnish, Swedish and English. These document templates take into account the child patient's developmental stage and level of understanding, the guardians' need for information and the laws regulating trials. These templates have been reviewed by the Finnish data protection ombudsman. The document templates are intended for the use of doctors and the pharmaceutical industry conducting clinical trials in Finland. The uniform documents are expected to improve the ethical quality of trials as well as speed up the time it takes for the medical and ethical authorities and the medicines agency to process trial statements and approvals at a national level. The IC document templates are currently accepted by all EC´s in Finland[11].

FINPEDMED TAILORED RESEARCH NURSE TRAINING PROGRAM

The latest development of FinPedMed is the Paediatric Research Training Program of four (4) Credit Units, which is specifically tailored for paediatric nurses working in Finnish University Hospitals. The curriculum has been designed by FinPedMed Executive Board together with the clinical research units and paediatric clinics of the University Hospitals and it includes many important issues around medical ethics; legal, regulatory, pharmacological, operational and pure ethical issues.

The main reason for this type of locally implemented training program was an urgent need of professional research nurses for paediatric clinical trials, as similar training does not exist in Finland. FinPedMed had faced challenges to hire personnel for new trials due to the annually low number of trials creating empty time gaps between the trials preventing to hire nurse replacements for nurses at clinics. For each new trial, the investigator need trained study nurse with research experience and knowledge. Additionally, the lack of knowledge

caused very limited communication about CTs. It is known that limited information among research personnel communicating with patients and families, lowers the interest to take part to trials and to conduct new trials. The new training program started as a pilot project in Tampere University Hospital (2015-2016) and since that in two other University Hospitals in Finland during 2016-2017. To date 30 newly trained paediatric research nurses have completed the training program together with Good Clinical Practice (GCP) test and medical, clinical, regulatory, ethical and legal aspects of paediatric CTs in Finland.

FUTURE TRENDS & PROSPECTS FOR PAEDIATRIC CTS

Finally, the most important part of the future trends and prospects will be electronically supported trial documentation and (partly) remote trial conduction. This "e-development" has started already in 2011[12], speeding the development of new guidance, legislation and research programs across the academia[13,14] pharma industry, regulatory authorities[15] and various types of companies specialized in electronic data and documentation. EU Commission has proposed a Regulation on Privacy and Electronic communication to update current rules for technical developments and to adapt them to the General Data Protection Regulation that will enter into force in May 2018. The objective is to reinforce trust and security in Digital Single Market[16].

The use of e-services and e-documentation together with social media in various forms is the most natural part of the life for current children and adolescents, known as "digital generation". The trend of future CTs will be in e-services in all formats leading to the increased need for new CT design, ePrivacy rules and new prospects for harmonized procedures and collaboration with all stakeholders – especially with Young Persons Advisory Groups (YPAGs). The YPAGs present the best consultants of the user-friendly and feasible digital e-applications of interactive multimedia patient information, as well as eICs and assents. These young people are the future and the e-development has started already.

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Children's participation in clinical research and bioethics policy-making: the experience of the Nuffield Council on Bioethics

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INTRODUCTION

The Nuffield Council on Bioethics is a UK-based think-tank which focuses on ethical issues arising out of developments in biology and medicine[1].

In June 2013, the Nuffield Council set up an expert interdisciplinary Working Party[2] to explore an issue that has represented a major challenge for those concerned with the health and healthcare of children and young people: *how can we ethically undertake the research[3] needed to ensure that their healthcare services for children are safe and effective, given that research often involves burdens and risks?*

The Working Party – which included members with expertise in ethics, clinical care, law, research, and public engagement – sought to address this question, while taking into consideration two competing points: first, that there is a desire to ensure that all treatments provided for children are based on good evidence; but, second, that there may be a reluctance to ask 'too much' of children, particularly when they may be unwell. These two points might affect children's welfare in contrasting ways: their welfare might be negatively affected by treatments and services that are not based on adequate evidence; but their welfare might also be undermined through exposure to risks and burdens inherent in clinical research processes.

Resolving these two welfare concerns, however, is a 'third factor': that is, the voice of young people themselves; and how their voice can be heard clearly and meaningfully in clinical research contexts; but also, for our own work, in making policy recommendations on paediatric research.

This third factor led the Nuffield Council to make a number of recommendations on children's and young people's participation in clinical research. Moreover, the third factor also encouraged us to involve children meaningfully in our own work. These two points are considered, respectively, in Parts One and Two of this paper.

BACKGROUND TO THE NUFFIELD COUNCIL'S PROJECT ON CHILDREN AND CLINICAL RESEARCH: ETHICAL ISSUES – *METHODS OF WORKING*

The Nuffield Council's project on *Children and clinical research: ethical issues* was launched in May 2015. Although the project was led by the Working Party, we sought the support and

guidance of young people, and their parents, throughout the course of our work through consultative and deliberative exercises (see *Part Two* of this paper for an overview of the involvement of young people in our work on this project).

Young people contributed to a range of project outputs, including a long report, an interactive magazine to summarise the report's findings for young people, an animated film, an online course for researchers, and a one-page summary with prompts for researchers who wish to involve children in their research[4]. During the project, a set of films were also produced to consider young people's perspectives on research ethics questions (*see Part Two (iii) below*).

PART ONE: THE NUFFIELD COUNCIL'S RECOMMENDATIONS ON CHILDREN'S PARTICIPATION IN CLINICAL RESEARCH

The Nuffield Council's overarching approach

The recommendations made by the Nuffield Council in its report *Children and clinical research: ethical issues* draw on our overarching approach to children's and young people's participation in research. There are several aspects to our approach.

The first is located in our firm belief that children and young people have a role in determining their own lives. Therefore, in the context of research, just as in other spheres of life, children from a young age should be understood not as 'subjects' of research, but as 'active participants' who are genuine partners in the research endeavour. This view is exemplified by our approach to shared decision-making in paediatric research contexts.

Consequently, instead of trying to second-guess what aspects of a particular health condition are of most concern to children and young people living with it, or what elements of a proposed study protocol might be unacceptably burdensome or distressing for them, researchers should ensure that the experiences and opinions of children and young people inform the development of their studies from the beginning.

Vulnerability

In clinical research contexts, concerns may be raised that children should be protected from research, because they are 'vulnerable'. However, we take the view that the time has come to protect children and young people *through* research not *from* research[5]. Moreover, an assumption that *all* children are vulnerable may stop worthwhile research from going ahead, and from progress with treatments and services for children's health being realised.

In order to minimise the risk that children may be placed in vulnerable situations, we believe that researchers must engage with children's and parents' views and experiences, and seek their input on research design, and research review.

Our overarching approach to young people's participation in research influenced strongly the conclusions and recommendations set out below.

Shared decision-making

We recommend that, where young people have sufficient maturity and understanding to make their own decisions about research participation (which the report refers to as

Case 3[6]), but are not yet treated as fully 'adult' by the law of their country, consent should, wherever possible, be sought from both the children and young people concerned, but also from their parents.

In cases where children and young people are *not* yet able to make their own decision (which the report refers to as Case 2[7]), we take the view that there is an ethical imperative to involve them in the research participation decision as much as possible. Requirements to 'seek' or 'obtain' assent from children who are being invited to take part in research should be understood as a requirement to involve children (as much as they wish and are able) in the decision about participation. This involvement should be recorded in some way, but it is the *process* of involvement that is ethically significant.

There may, of course, be situations where children or young people are not able, at this time, to contribute their own views as to whether or not they should take part in clinical research; this may include babies or very young children, but also children who are temporarily unable to contribute because they are very unwell or unconscious (the report refers to this circumstance as Case 1[8]).

Developing and reviewing research protocols

Developing research proposals

The Nuffield Council draws particular attention to the role of Young Persons' Advisory Groups (YPAGs) in contributing to the development of research protocols for studies that aim to include children. The role of the nine YPAGs across Europe provides vital support in this endeavour by offering researchers a meaningful opportunity to engage with the voices of young people on their proposed study protocol. In addition to commenting on elements of the study protocol itself, YPAG members also advise researchers on the appropriate design of patient information sheets and consent and assent forms. YPAG members may, for example, advise researchers on how terminology might be modified to make their written materials more accessible for young people; or urge them to produce different versions of those written materials for different age groups.

However, in addition to support offered by YPAGs, for some protocols, it will be important for researchers to seek input from children, young people, and parents with personal experience of living with a particular condition.

The practical importance of involving children and their parents in developing research protocols was highlighted us during the evidence-gathering phase of our project by the British Medical Association: *"Involving parents and children in the design of studies, wherever possible and relevant, could also help to encourage recruitment and retention."*

Reviewing research proposals

Our conclusions include the view that, in order for RECs to be well-placed to make a decision as to whether the particular risks and burdens levied by a research protocol can be ethically justified, it is essential for them to have access to appropriate expertise. In our report, the role of professionals with specialist knowledge is noted as one form of expertise. However, this section of the paper focuses on the expertise that RECs should access (directly or indirectly) from the participation of children, young people, and their families.

Drawing on our conclusion that concerns about the 'vulnerability' of young research participants can be countered by a partnership with children, young people, and their parents, we recommend that RECs ensure that the voice and expertise of young people are taken account of. This expertise is particularly important when RECs are concerned about the potential impact of any of the procedures involved in the study protocol on children's day-to-day lives.

The Nuffield Council's report also suggests that RECs should routinely expect researchers to have involved children, young people, and parents, as appropriate, in the design of their studies. RECs will therefore be able to draw on the reported opinions of these groups in order to assure themselves whether the study design is appropriate; whether any risks and burdens have been minimised and justified; and whether information materials are comprehensible to their target audience. Researchers who have not sought input in this way should be required to justify to the REC why this was not appropriate in their case, and be able to demonstrate an appropriate knowledge of relevant literature and guidance.

PART TWO: YOUNG PEOPLE'S PARTICIPATION IN THE NUFFIELD COUNCIL'S PROJECT ON *CHILDREN AND CLINICAL RESEARCH: ETHICAL ISSUES*

This section of the paper briefly summarises four examples of the support offered by young people's participation in our project on ***Children and clinical research: ethical issues***[9].

1. Workshops and interviews

Stakeholder group workshops

One form of support was that offered by a stakeholder group involving young people and parents, from which the Working Party sought advice not only when drafting its consultation document, but also when drawing up its recommendations and conclusions, and generally as a 'sounding board' throughout the project. This group was established after the Working Party's first meeting[10], when it became clear that our work would be improved through working with young people who were, after all, at the very heart of our project.

Interviews with YPAG members

Ahead of the production of the interactive 'magazine' version of the report (*see also point (2) below*), interviews with members of the Liverpool YPAG were undertaken in order to provide audio content for the magazine, and to bring the content 'to life' through young people's own voices.

The interviewer encouraged participants to respond to a range of questions including: 'Who do you think should make decisions about children taking part in research?', and 'How would you describe the 'perfect' researcher?'[11] The final recordings were embedded into the final version of the magazine, and provide further context to its contents.

2. Written input

We sought young people's written input in a variety of ways during the course of this project.

For example, the launch of the report's consultation documents included an online survey aimed at young people. Young people's responses to this survey influenced the project, and their views can be seen throughout the final project report[12].

Further written input from young people was sought to support drafting of the magazine version of the report. Draft versions of the document were given to YPAGs in London, Liverpool, Scotland, and to the KIDS group in Connecticut to ask for feedback on its layout, language, and general accessibility. The feedback from the young people was invaluable, and resulted in a final version of the magazine that was significantly shorter than earlier drafts, more visually appealing, and included improved signposting to enable young people to identify parts of the document that were of particular interest to them.

A young person with whom we worked as part of our Youth REC film project (*see (3) below*) also agreed to review its report, along with professional stakeholders. Other young people from the Youth REC film project also contributed blog posts to the Nuffield Council's website[13].

3. Film participation

Live action films

In addition to contributions from young people who responded to the Nuffield Council's online questionnaire (*see (2) above*), the Working Party also identified a need to engage with young people *without* direct experience of clinical research. Particularly, the Working Party were keen to compare young people's views on research ethics questions with those of adults with research ethics expertise. Subsequently, a film project on Youth RECs was established and, with the help of the Nuffield Council's stakeholder group, and academic collaborators, workshops were organised which involved young people aged from ten to 18 in three schools in the south of England; and also with a group of adults who formed a fictional REC for the purposes of the film. Each of these workshops were filmed by a documentary filmmaker.

Both the adult group and the young people's groups were asked to discuss the same fictional research protocol, which focused on a new way of treating children with asthma. Like other RECs, each group was asked to consider the ethical implications of the fictional study.

The final films[14] highlight, importantly, that young people without prior knowledge of clinical research processes are more than capable of considering the same research protocol as a group of adults, provided that the content of the protocol is presented appropriately (for example, through summarising key parts of the protocol in terms which are age-appropriate).

Animation

In order to prepare for the launch of the project, we visited a YPAG based in Liverpool, UK, to ask members how we might best present our report.

The young people advised that one project output should be a short animated film which summarised, for young people over the age of ten, the report's key messages.

We adopted the young people's advice and subsequently engaged the services of an animation company. With the animators, the Nuffield Council organised a workshop where young people (from YPAGs, our stakeholder group, and schools and colleges with which we had previous contact) met to discuss a range of issues in order to stimulate visual content

ideas for the animation. Facilitators (Nuffield Council staff and producers from the animation company) invited participants to consider questions including: 'when you think of a typical researcher, what do you imagine them being like?'; and 'when you hear the term 'health research', what does it bring to mind?' Participants were particularly encouraged to describe and draw images that occurred to them during the course of the workshop. This approach elicited vivid content, which contributed to an engaging final animation[15].

CONCLUSION

It is only through the involvement of young people in clinical research that a balance can be struck between the risks and benefits of research. As our recommendations highlight, young people's participation must be considered by all stakeholders who are involved with paediatric research. From our own experiences of working with young people throughout our project, and the overwhelmingly positive impact their participation made to our work, we would also argue that their involvement is equally vital for policy-making too.

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15. For example, including the image of an-out-of-control rollercoaster to represent the concern that once a research participant agrees to take part in research, they may be worried that they cannot stop. See: Nuffield Council on Bioethics (2015) Health research: making the right decision for me, available at: https://www.youtube.com/watch?v=6yaKwLG_vlE.

9 "Ethical problems in the clinical trials and use of medical devices. The example of fetal surgery" What may bring the next European Regulation?

Pablo Ferrer Salvans
REC of Saint John of God Foundation - Borja Institute of Bioethics.

PRESENTATION OF THE 4TH ROUNDTABLE

First at all I would like to thank all attendants for being here today in this Congress of Research Ethics Committees (RECs), a body that plays a very important role in the development of biomedical research. Your presence here and your interest is the best reward we can receive for our work. In the last few years RECs have entered critical times, because they represent the weakest link in the chain of assessment of research projects. They must now face very deep legislative changes, without having either enough time or resources to look for adequate and ethical solutions.

As moderator of the fourth roundtable of this European Congress of Research Ethics Committees it is my great honor to introduce to you the speakers who have agreed to talk to us about the clinical trials with medical devices, considering some of the main traits of the new European Regulation on hand as with the example of fetal surgery. What I will deal with represents the point of view of a usual member of a REC.

It is my pleasure to now introduce Xavier Canals. He has received his education as an Engineer in Information Technologies. Currently, he is the Director of his own enterprise "Tecnomed Ingenieros" located in Barcelona, he is also Professor at ESADE School of the Ramon Lllull University. He belongs to several scientific societies and he is the Vice chairman of the Spanish Society of Electromedicine, Medical and Clinical Engineering (SEEIC Sociedad Española de Electromedicina e Ingenieria Clinica). He is also President Member of AENOR Standardization Committees. He acts as consultant on Medical Devices development and we have asked him to tell us how he would advise a medical devices promoter to apply for a research project.

I am also pleased to present Saskia de Weerd-Hamer. She comes from the Netherlands and she has an impressive CV, always being in the frontier of innovation. She has been a Head of Department VCMO at St. Antonius Hospital Nieuwegein and head of an accredited Regional Medical Ethics Review Board. She has participated in several workshops and meetings on the development of medical devices assessment and clinical trials approval. She has been the lawyer of several private research companies. Currently she is Head of Department at the University Medical Centre of Utrech in the Netherlands, and she leads the secretariat for the Research Ethics Committee, the Biobank Ethics Committee and the Committee for

Animal Experiments. She is responsible for the management of the Department and advise about the strategy of the Committees. She is a member of the Management Team of the Directorate "Quality and Patient Safety" of the Hospital. We have asked her to share with us us some of her experience in the assessment of clinical trials with medical devices.

Finally I am proud to introduce Eduard Gratacós. He is director and professor at BCNatal, a referral centre in Maternal-Fetal Medicine at the University Hospitals Clinic and Sant Joan de Déu in Barcelona, and of the Fetal Medicine Research Center (Fetal i+D), a multidisciplinary team with one of the largest scientific international productions. Founder of Fetal Medicine Barcelona, a non-profit organization supporting worldwide training, with +7,000 healthcare professionals linked, masters and topical courses, and solidarity projects to improve maternal-child health. Expert in fetal medicine and therapy, with over 1,800 fetal surgeries. Director of European Commission PhD programme Erasmus Mundus in Fetal Medicine, offered jointly in Barcelona, Leuven (Belgium) and Lund (Sweden). He has published +400 peer reviewed papers, and has directed 35 national and international research projects and 25 doctoral theses. We have asked him to share with us some of his surgical experiences with medical devices.

They will now give their presentations just when the new European Regulation on Medical Devices has appeared. (We will not consider the regulation of In Vitro Diagnostic Devices). The reference document on Medical Devices (MD) is dated 5th April 2017 and is now made up of 566 pages, 316 as main legislative text and the rest in XVI annexes to further developing very important issues, for instance Annex XV on Clinical Investigations or Annex VIII on The Classification Rules for medical devices. The previous similar document of the Council of the European Union that could be worked through had only 352 pages including all annexes, and corresponds to the 27thh June 2016. The Regulation is made up of 10 Chapters with 123 Articles and the aforementioned additional XVI Annexes. Obviously, a great deal of time and effort is required to understand these immense documents and clearly within the ten minutes of a roundtable presentation it is impossible to deal completely with such huge legislative text.

What we will try to do in the short time we have available, is to highlight some points that may help in the understanding of the clinical trials or the research projects with medical devices, and also focus on some particularities that make them different to the clinical trials with drugs or other research projects. The first point to comment on is the different way of action of medical devices (MD) compared with the way of action of drugs. The latter acts through the drug-receptor theory, the mass-action kinetics, the log-concentration-effect curve and all issues related with the several interpretations of the drug-receptor binding theory. Because of all these complex interactions there is a big variability in the results and the variables showing the effect of drugs are usually probabilistic variables. With the medical devices, many times the relationship is all or none because the more physical way of acting, and the relationship with the variables showing the effect is a deterministic one. The biological variability is also superposed. A detailed description of this technology evaluation may be found at http://www.knaw.nl/en/news/publications/evaluation-of-new-technology-in-health-care-1?set_language=en

A corollary of what has been just described is the way to explain the effects. The effect of a medical device may be described in advance through several specifications, characteris-

tics of the device, that have been the basis of their design. This is the reason why it may be possible to confirm the effectiveness of a medical device with a technical verification that gives witness to the right functioning of the device. This task has been assigned to special structures named "Notified Bodies" that are fully described in the Regulation Chapter IV.

There is the possibility that a MD accomplish exactly all their specifications but does not function in their clinical applications. This is the reason why clinical testing is necessary before making them available to patients and the justifying of the new Regulation. It is made up of ten chapters (Reduced descriptions):

0. Scope and definitions.
i. Making available and putting into service of devices.
ii. Identification and traceability of devices. European databank on medical devices.
iii. Notified bodies.
iv. Classification and conformity assessment.
v. Clinical evaluation and clinical investigation.
vi. Post Market surveillance, vigilance and market surveillance.
vii. Cooperation between Member States. Medical Device Coordination Group.
viii. Confidentiality, data protection, funding, penalties.
ix. Final provisions.

The new Regulation represents an integrative effort putting together previously accepted rules. The new Regulation takes into account the Helsinki Declaration, the European Convention on Human Rights and Biomedicine, and many other already accepted international standards in biomedical research.

In the chapter of Scope and Definitions it is important to note that the terminology is nearer to the ISO Standards than to the Good Clinical Practices. The protocol receives the name of "Clinical Investigation Plan" and some of the Standard Operative Procedures have been replaced by ISO Standards. These changes will hopefully represent something more than simple routine changes, but rather encourage the trend to work with at more open standards systems. Examples are the EN-ISO 15155 on Clinical Investigation, the UNE-EN-ISO 14971 on Risk Management and the UNE-EN ISO 10993 on Biological Evaluation of Medical Devices and many others that will show themselves when making an in-depth study of the new Regulation. In the domain of Good Clinical Practices there are procedures which have been agreed with the ICH but there are also Standard Operative Procedures that are the private property of sponsors, and it is very difficult to have access to them. Surely it would be of great worth in next few years to harmonize the worlds of ISO and GCP.

The new Regulation considers the Helsinki Declaration, the informed consent, the vulnerable populations and many other ethical issues. But to be short: for the clinical evaluation of medical devices the responsible bodies are the RECs, but their regulation is left to the criteria of Member States instead of being regulated with the same scrutiny as occurs with Notified Bodies. There is a contrast with the refined description of Notified Bodies where it lays the main weight of medical devices assessment. Perhaps it would be worth changing the way we think of the organization of RECs and begin regarding them with a similar importance to the Notified Bodies as they contribute to the assessment of the clinical trials and clinical experience with the MD.

To end my round table presentation I feel that I must make reference to article 15 "Person responsible for regulatory compliance", a task that RECs have developed over many years. The article 15.5 says "The person responsible for regulatory compliance shall suffer no disadvantage within the manufacturer's organization in relation to the proper fulfilment of his or her duties, regardless of whether or not they are employees of the organization." (Page 97). This sentence is full of wisdom and perhaps we should reflect deeply on it, extending its scope to the whole research community.

Without further delay it is my great pleasure to give you....

10

What are the challenges with regard to medical devices, how we deal with these challenges and what will the future bring? The Dutch approach

Saskia de Weerd-Hamer

Head of Department for the Medical Research Ethics Committee (MREC), the Biobank Research Ethics Committee and the Committee for Animal Experiments, University Medical Centre Utrecht, Netherlands.

A GENERAL OUTLAY ON THE DUTCH APPROACH

In order to understand the Dutch approach on research with regard to medical devices[1], it is necessary to know more about the Dutch approval system for research in general.

The Dutch review system is unique within Europe. In consists of a decentralized system with integrated approval. Clinical research that falls within the scope of the Dutch law: WMO (is Medical Research involving Human Subjects Act) must be reviewed by an accredited MREC. There are twenty-three accredited Medical Research Ethics Committees (MREC's) and one Central Committee (CCMO). There are very strict rules for MREC's and its members in order to meet high quality standards. The MREC reaches its decisions independently and is by law an independent governing body. The MREC's have legal jurisdiction to make decisions that are binding to citizens (in this case, decisions on the basis of the WMO.

The CCMO has several roles; it checks if an MREC meets her obligations for accreditation and oversees the operations of MREC's. Furthermore she is the Competent Authority for research with medicinal products. The CCMO also acts as a MREC for specific types of research stipulated by law. The majority of the research however is reviewed by MREC's. The primary task of a MREC is to protect the participants of a trial. As a consequence of this system, a MREC in the Netherlands has more responsibilities than MREC's in other Member States.

THE DUTCH APPROACH WITH REGARD TO MEDICAL DEVICES

A few numbers with regard to the types of studies; the number of clinical studies with medical devices has increased from 180 in 2012 to 218 in 2016 what accounts for about 13% of al research in the Netherlands. As opposed to studies with medicinal products: 542 in 2012 and 582 in 2016 what accounts for a third, and has been at this percentage level for years.

There are about 200 new medical devices a year in the Netherlands, of which 30% falls within risk class 2B and III (clinical research obligatory), 20% is without CE registration.

The Dutch, have another unique situation. Opposed to the other European countries in which the Competent Authority (CA) approves the product information after approval of the MREC. In the Netherlands, the MREC is responsible for the approval of a medical device trial including the product information.

After this approval by the MREC of medical device trial, the manufacturer of the medical device in question has a number of legal obligations before the clinical trial may start. One of the explicit conditions is the submission of both the study as well as a positive advice of an accredited MREC to the Dutch Health Care Inspectorate. This applies to manufacturers who are responsible for the development of a medical device with the intention of eventually marketing this medical device. This review not only takes place on the basis of the Medical Research Involving Human Subjects Act, but also is specifically prompted by the legislation regarding Medical devices. This Dutch medical device legislation is based on European legislation.

The MREC reviews the clinical trial. The competent authority for medical devices (Inspectorate) has mainly an overseeing role concerning this kind of studies. This current system is expected to remain in place in the future. This means that the MREC must have the expertise to review the entire research dossier. Most Dutch MREC's have a medical physicist at their disposal either as a member of the MREC or as an advisor. It is to be expected that the number of medical physicist connected to MREC's will increase in the future. Furthermore it is wishful and important that the exchange of expertise between the different MREC's is facilitated.

THE DUTCH POSITION ON MEDICAL DEVICES WITH A MEDICINAL PRODUCT

Considering the different legal requirements for medical devices and medicinal products, it's important to estimate the scope of a product. A drug eluting stent for example is a combination of both; it is a medical device with a medicinal product. The CCMO considers medical devices combined with medical products as a medicinal device as long as the effect of the medicinal product has a subordinate function with regard to the function of the medical device.

CHALLENGES FOR MREC'S WITH REGARD TO MEDICAL DEVICES

One of the major challenges for MREC's is the specific expertise to review medical devices. How can we guarantee sufficient expertise in MREC's, regarding the quick developments and the large difference of types of devices? And how can we share this expertise on national and European level? Perhaps existing European networks could play a role in this respect.

The new legislation requires more clinical evidence, so the number of clinician trials with devices will increase rapidly.

A lot of the MREC's have a medical physicist at their disposal. A medical physicist often looks at the ISO norms, but has insufficient expertise of the implications of the new device for the patient. And how independent is this medical physicist for the MREC if he/she also made an internal report for the hospital with regard to the same medical device?

Another struggle is to assess if something should be regarded as a medical device as defined in the legal definition. And the interpretation of the risk classes also leaves room for discussion. As the classification stipulates the required procedure, the stakeholders may be biased to a lighter classification.

Another issue is the large diversity of medical devices, which requires specific expertise of the MREC and Competent Authority.

In the Netherlands, the different roles and responsibilities of the MREC's, CCMO and Inspectorate is another point of attention. This will and needs to be clarified in the near future. The Inspectorate organized a conference to discuss this topic with the focus on clear communication between Inspectorate, CCMO and MREC's, consultation and cooperation.

In the Netherlands the CCMO will play a more coordinating role in the future in line with the new EU Directive for medicinal products.

A complex point for approval of devices is when software is part of the devices. Guidelines on the qualification and classification of stand alone software used in healthcare within the regulatory framework of medical devices at this point can be found in the MEDDEV[2].

WHAT BRINGS THE NEW LEGISLATION AND HOW DO WE DEAL WITH THIS/ POSITION OF THE MREC?

On May 25th 2016, the Council and representatives of the European Parliament agreed on new rules on medical devices and in vitro diagnostics (under Dutch presidency).

On April 5th 2017, the European Parliament adopted the two regulations: a regulation for medical devices (2012/0266 COD) and a regulation for in vitro diagnostics (2012/0267 COD).

The negotiations about this new legislation started in 2012, so it has been a lengthy process, which was needed to achieve new EU law.

The new legislation will cause changes in the system of research, registration and post marketing surveillance in the field of medical devices and in vitro diagnostics.

The aim of this new legislation is to modernise the current legislation to make sure that medical devices and in vitro diagnostics are safe, can be traded across Europe and that new innovative devices reach patients in time.

The recent scandals related to faulty silicone breast implants or metal artificial hips have strengthened the need to update the current rules. The new legislation entails some significant changes that will be summarised hereafter.

SIGNIFICANT CHANGES

- *Stricter requirements* for medical devices (with regard to clinical evidence, registration, rules for Post Market Surveillance, vigilance and market surveillance);
- *Identification and traceability* of devices;
- *Scope;* change in definitions resulting in products that are currently not classified as medical devices or accessories under the MDD, are now included in the scope of the

MDR. The MDR will apply also to non-medical devices with a risk profile similar to medical devices (like contact lenses and cosmetic implants);
- *Quality system* and its resources; regulatory compliance officer within organisation, a supply chain regime, liability of the various operators), relabeling and repackaging regime;
- *European databank* on medical devices (EUDAMED) for traceability, registration of devices and publication of information concerning medical devices on the EU market. For the first time also accessible for healthcare professionals, end users and the general public will have access to certain parts of the information;
- *Unique devices Identifiers* (UDIs) for all devices;
- *Notified bodies*; supervision will change considerably and all notified bodies will need to apply for a new designation;
- *Classification rules will change* for certain devices, these devices may need to be recertified in another (higher) risk class (impact nanotechnology, specific orthopaedic implants, AED etc.);
- Changes in conformity assessment rules;
- A summary of clinical evaluation will be *publicly available* for high-risk devices and permanent implants. Clear evidence will need to be provided in layperson's terms;
- *Cooperation* between member states, a Medical Device Coordination Group, EU reference laboratories, expert panels and devices registers (more centralized governance structures, groups of experts will write a growing number of guidance documents and minimum requirements);
- Confidentially, data protection, funding, penalties;
- Patients have to be informed about the consequences of DNA tests.

HARMONISATION

In October 2016, The Joint Research Centre (JRC) organised a European workshop about Clinical research with medical devices. The goal was to exchange experiences between Competent Authorities in order to harmonise procedures for the review of clinical research with medical devices. The member states all reviewed the same protocol (first in men study with a high risk medical device) and came together in this workshop to discus the similarities and differences in their findings.

An additional finding during the discussion was that the tasks of the MREC's differ per member state. Furthermore it seemed that competent Authorities not always have total clarity on the tasks of their national MREC's and how they operate. As this might pose a risk, therefore prior to harmonisation transparency on national level is a must.

The other MS's have to trust that there will be a good and entire review by a MS. A well-harmonised procedure will contribute to guaranteeing the quality and completeness in all MS. The JRC considers to further inventory what is needed to achieve a harmonised procedure that can be used in all MS's.

In the new procedure one MS will be coordinating the review of a study with medical devices. This is in line with the new EU Directive for medicinal products. There are a lot of similarities between the new EU legislation for medical devices with the rules for research with medicinal products, EU direction (536/2014).

NEW DEVELOPMENTS, WHICH ARE THEY AND HOW DO WE DEAL WITH THEM?

Today's medical innovations and technologies in general and innovative medical devices in particular are becoming more and more important. The number of medical devices for diagnosis, monitoring and treatment is large and this number continues to grow. There are more than 500.000 medical on the market. It is estimated that in 2060 there will be twice as many Europeans aged 65 or older. This increases the importance of medical devices for public health and medical care.

The use of e-health in clinical research appears to be difficult in practice and causes a lot of questions for different stakeholders involved. What is the definition of e-health? After approval by the MREC, long legal pathways occur and delay the start of studies. Questions about privacy and data protection for example are difficult to answer with regard to e-health solutions.

Another question is how to address the added benefits of medical devices.

"It is quite difficult to evaluate whether a new medical devices offers any advantages, and what those advantages are. After all, there is more involved than technical quality and safety. Any evaluation also has to consider the varying usage and user requirements, sector specific guidelines and legislation. The report[3] aims to offer the various stakeholders guidelines for selecting the research method that best suits the relevant medical device, including post marketing surveillance. Benefits can include direct therapeutic effect, but also indirect benefits". The report is meant as a wake up call and shows that there are different ways of tackling such evaluations, and that a 'one size fits all' approach is insufficient.

A randomised control trial (RCT) is often not necessary for research with medical devices, only if it concerns therapeutic devices (like stents, robot surgery). About 90% of devices are non-therapeutic (like diagnostics, monitoring). These kinds of devices often generate information for medical intervention, and are indirectly therapeutic.

The above mentioned report advised to create a platform for all stakeholders involved in a devise, so as they can develop a good plan of action to evaluate and implement a study. This advice was implemented at the University Medical Centre Utrecht, the Netherlands and is called "Thinc". (The Healthcare Innovation Centre Utrecht). After recent evaluation national implementation is the due course of action.

CONCLUSION

Medical technology plays an important role in healthcare. Guaranteeing patient safety with regard to medical devices is important, without curtailing medical innovation. New legislation is needed to protect patients and prevent scandals as happened in the past. The new EU Directive is a big step forward.

To fully utilise the restricted expertise in the wide range of device technology the use of national and international specialists is necessary. I recommend using the EURECNET network to create a list of experts in the field of devices that can be consulted. The future challenges call for more cooperation and harmonisation.

SOURCES

- http://www.europarl.europa.eu for the new directives on medical devices.
- Website of the Central Committee in the Netherlands (www.ccmo.nl)
- White paper of the BSI Group: How to prepare for and implement the upcoming MDR-Dos and don'ts
- KNAW (2014). *Evaluation of new technologie in health care. In need of guidance for relevant evidence.* Amsterdam, KNAW.

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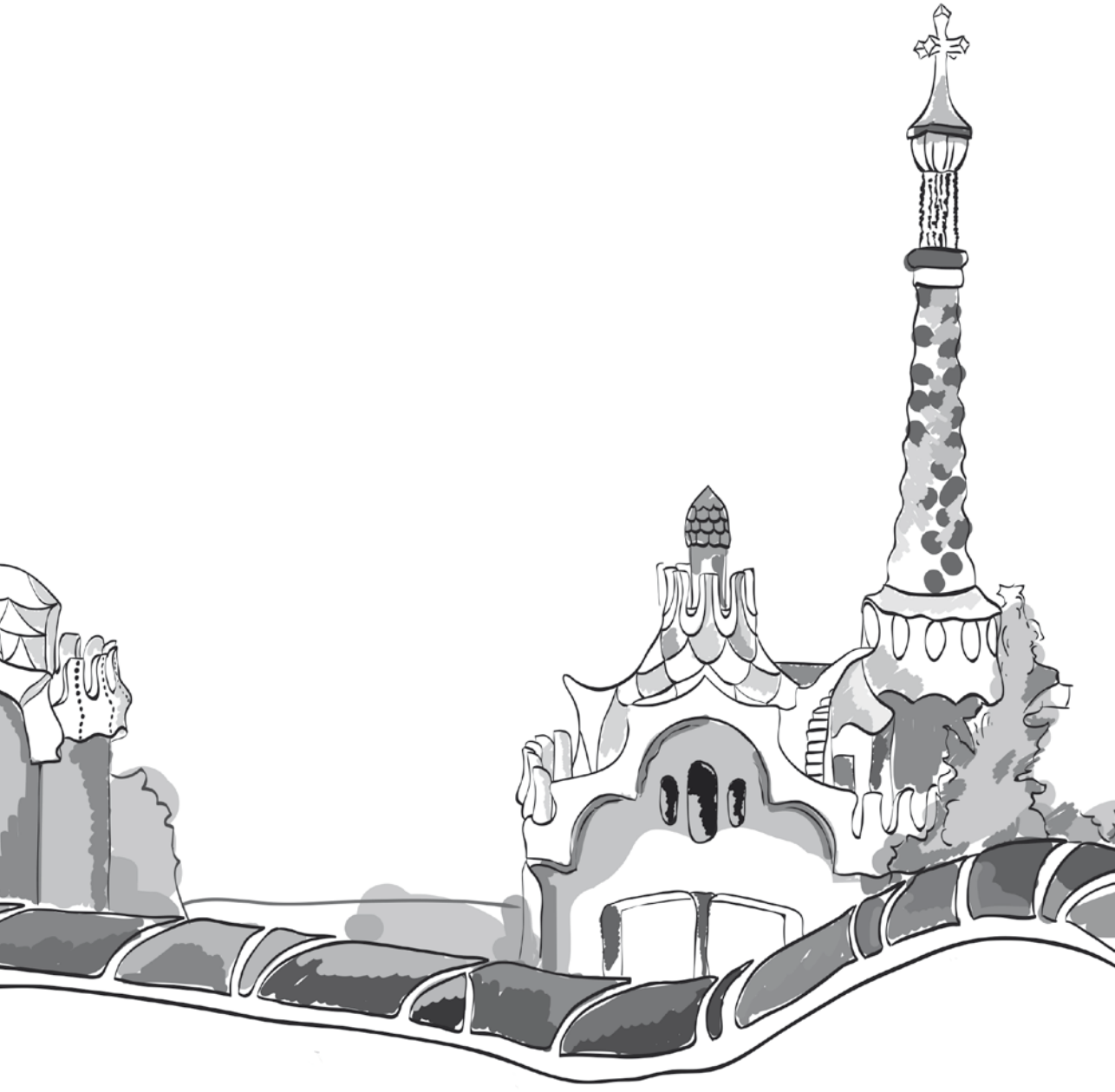

COMUNICACIONES

The revised CIOMS guidelines and implications for Research Ethics Committees

Rieke van der Graaf
Secretary Working Group Revision CIOMS guidelines.

ABSTRACT

The Council for International Organizations of Medical Sciences (CIOMS) has recently published its revised International ethical guidelines for health-related research involving humans.

Progress towards a world where all can enjoy optimal health and health care is crucially dependent on all kinds of research including research involving humans. Involving humans in medical research is necessary to improve the knowledge base on which medicine should be based. At the same time, individuals participating in health-related research have individual human rights and have a right to be protected against the risks that research may bring to them. The tension between these two considerations has led the medical community to endorse ethical guidelines for health-related research. Research Ethics Committees can use these guidelines to evaluate whether a given research protocol is ethically acceptable or not.

CIOMS, in association with the World Health Organization, started its work on ethics in health-related research in the late 1970s. Accordingly, CIOMS set out, in cooperation with WHO, to prepare guidelines to indicate how the ethical principles set forth in the Declaration of Helsinki of the World Medical Association, could be effectively applied, particularly in low-resource settings, given their socio-economic circumstances, laws and regulations, and executive and administrative arrangements. Since then revised editions of the CIOMS ethical guidelines were published in 1993 and 2002. New developments in research have prompted CIOMS to again revise their ethical guidelines. The result is now available in this new publication.

In the new 2016 version of the ethical Guidelines, CIOMS provides answers to a number of pressing issues in research ethics. The Council does so by stressing the need for research having scientific and social value, by providing special guidelines for health-related research in low-resource settings, by detailing the provisions for involving vulnerable groups in research and for describing under what conditions biological samples and health-related data can be used for research.

In this presentation I will emphasize the implications of these revised guidelines for Research Ethics Committees. I will focus in particular on the guidelines on "vulnerable populations" and groups in need of special protections: children, women, incompetents, pregnant women, and populations in LMICs.

Latin American research ethics committees: Whose interest do they serve?

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INTRODUCTION

The outsourcing of Clinical trials (CTs) to Latin America (LA) began in the mid-1940s under the sponsorship of universities and the National Institutes of Health (NIH) of the United States (US). The number of studies was relatively low and remained stagnant until the late 1990s, when the pharmaceutical industry started outsourcing CTs to the region[1]. Peru is a good example of the trend, only one clinical trial was approved in 1995, by 2009 the number of approvals reached 150[2].

The history and experience of LA research ethics committees (RECs) is quite short, but during these 25-plus years we have seen many changes in the regulations that determine their organization, mandate and performance[3].

No CT should start without the approval of at least one registered REC. Protocols need to adhere to national regulations and internationally recognized ethical principles. Similarly, RECs are responsible for ensuring that CT are appropriately implemented and respect the human rights of the subjects. In decentralized countries (i.e. Argentina) the regions can establish additional regulations compatible with the national framework[4].

We examine some of the issues faced by LA-RECs, their needs, performance and future, in view of increased complexity of CT designs and health technologies.

This paper draws on ten years of field work, archival information and extensive conversations with researchers and regulatory agencies (RAs).

LEGAL, STRUCTURAL AND RESOURCE CONSTRAINTS

RECs are registered by an agency within the ministry of health, most often the RA of pharmaceuticals. A few countries have an accreditation system. Registration and accreditation criteria focus on structural issues and do not evaluate RECs' capacity to evaluate the scientific and ethical aspects of CTs sponsored by the pharmaceutical industry[5].

There are several types of RECs. Except for Panama and Brazil, countries allow the presence of private RECs, which are often labeled as 'independent', but we prefer to call them

commercial. Panama and Brazil have national RECs able to reject the implementation of CTs previously approved by institutional RECs, which are the most common and are supported by the establishments that conduct CTs, mainly hospitals and universities. In some countries, Contract Research Organizations (CROs) and even the pharmaceutical industry (in Mexico) have established their own RECs[5,6].

More and more, for reasons that will be explained later, the pharmaceutical industry prefers commercial RECs.

Regulations differ from country to country, and are undergoing frequent changes. But progress--meaning more rigorous frameworks incorporating internationally accepted ethical principles— often go one step forward and two steps backwards. This was the case in Argentina, with ANMAT Regulation 6677/10 of 2010, and Peru's complete reversal of the progressive regulations approved in 2006 and rescinded the following year by Supreme Decree DS-006-2007 SA[2]. More recently, the Brazilian Medical Association severely restricted the use of placebo in CTs, but was largely ignored by RECs[7], and there are reports that the national REC is about to disappear.

LA RECs often approve placebo-controlled CTs when alternative treatments exist, non-inferiority CT designs and CTs for marketing purposes. The budgets of the CTs are seldom included in the protocols reviewed by RECs.

Resources and training

RECs function with very few resources. Not all RECs have a secretary, archival space or a dedicated computer. Only those located in large hospitals have access to scientific literature, seldom do they have the support of CT methodologists or statisticians, and few include members with broad knowledge and expertise in clinical research ethics, that is, beyond having some training in Good Clinical Practice, or the completion of the US NIH or CITI training courses. The RECs' composition is often skewed, clinical researchers –not necessarily experts in the technology to be tested- are overrepresented to the detriment of CT methodologists or community representatives[5].

No minimum training requirements for REC members have been established in any country. In some cases, a certain proportion of REC members must complete either the NIH or the CITI course. Some countries have training manuals, but whether and how often they are used remains unknown[5].

Members of institutional RECs are not compensated for reviewing CT protocols, and some RECs approve industry-sponsored protocols under the false premise that they have approved by the Food and Drug Administration of the US (FDA) or by the European Medicines Agency (EMA) or other regulatory agencies (RAs). They ignore that RAs do not evaluate the ethical aspects of CT protocols.

RECs tend to function in silos, with very little -if any- communication among them on the ethical dilemmas embedded in the scientific and methodological aspects of specific CTs. RECs have great difficulties in finding experts to help resolve those dilemmas, for multiple reasons, including confidentiality requirements and the availability of experts without conflicts of interest[8].

In general, the minutes of RECs' meetings are confidential. While all countries have a registry of approved CTs, none have a public record of rejected CT protocols.

CONFLICTS OF INTEREST

RECs' independence from the sponsoring industries and CT researchers and the institutions or universities where they are to be implemented, have been questioned[9]. Independent-commercial RECs are all but independent. They know that if they request too many changes, take too long to review a protocol, or worst, decline its approval, the sponsors will quickly find another commercial REC and they will go out of business. In Argentina over 60% of the protocols are approved by two commercial RECs[4] and in Peru one commercial REC approves about 40%[10].

Some commercial RECs approve protocols in two or three days. There is no information on the speed of approval or protocol changes required by RECs attached to CROs, private research centers or the industry.

Although regulations clearly state that RECs must be independent from site managers, in practice, hospital managers and universities often express strong interest in CT approvals. Implementing CTs enhances the site's reputation, increases its equipment and other resources, and facilitates the treatment of patients who otherwise would go untreated.

In LA, principal investigators (PIs) generate incomes far greater than their regular salaries and those of their colleagues. PIs and co-PIs benefit from industry-sponsored CTs in many other ways, including paid trips to international conferences, speaking fees, and signing ghost-written papers[11].

All these perks contribute to PIs' prestige and power among colleagues and professional associations, and indirectly influence RECs decisions and the attainment of favors within clinical establishments, which can lead to abuses. On several occasions, site managers have overruled the REC's decision to reject a CT protocol and have allowed the use of scarce public resources to benefit CTs to the detriment of other patients. There are reports of PIs approving their own protocols, and RECs established at hoc to approve a specific CT[11].

The speedy approval and implementation of CTs is of outmost importance for the pharmaceutical industry. The sooner the CTs is completed, the longer the period of market exclusivity of the new product[12]. In the case of blockbuster medicines, each day of market exclusivity represents as much as US$ 8 million in sales.

THE CONSEQUENCES OF RECS LIMITATIONS

Even if RECs managed the conflicts of interest, and had the ethical and scientific capacity to evaluate the CT protocols sponsored by industry, there are several aspects that would remain beyond their control.

1. Supervision of CT implementation

Due to lack of resources, institutional RECs cannot supervise the implementation of CTs.[5] Without supervision, they cannot identify, among others, if subjects are unwillingly retained in CTs, if side effects are reported and properly and timely investigated, if the care subjects receive complies with ethical principles and respects their human rights, if data are appropriately handled, if subjects comply with physicians' recommendations, and if there

have been deviations of the CT protocol. All these problems—and we have mentioned only a few—have been documented after the death of subjects or through whistleblowers.

Commercial RECs may occasionally visit the sites but do not interview subjects. Visits are limited to verifying that the inform consent has been signed but not if it has been understood[13]. Inspections are at best administrative task, since most RAs do not have the power to stop a CT or to issue fines when they identify CT irregularities.

2. Accessibility to products after their approval and commercialization

The ethical principle that testing should not be done in communities unlikely to benefit from the experiment is well accepted. A recent study found that, for commercial reasons, the pharmaceutical industry had not always registered or marketed the products tested in LA two years after they had been approved and commercialized in the US. The study also documented that drugs tested and sold in LA were unaffordable to all but the upper wealthiest decile[14].

Before trials begin, the pharmaceutical corporations know the price to be charged, which is unrelated to production costs. RECs should have this information to evaluate if the product will be affordable to patients and health care payers. If not affordable or no information is provided, the protocol should not be approved. Ideally, independent experts should establish affordability thresholds for modern technologies.

3. Verify the real objective of the CT

It is also known that the main objective of some CTs is to market the product to key practitioners. The sponsors hide this information in ways that RECs cannot uncover. It has been documented that a very large proportion of the drugs tested in LA do not add therapeutic value to the existing arsenal and, according to independent experts from high-income countries, have significant side effects and should not be used[14]. When highly specialized researchers study CT protocols they can raise some red flags, and are likely to identify if the CT is necessary and its likelihood of success, given the results of pre-clinical and other clinical studies and other pharmacological information. This is an impossible task for most LA RECs.

4. Informed consent

In LA, consent forms are generally signed, but few subjects understand them. Subjects are recruited among the poor by physicians working in the public sector and have limited medical literacy. Referring physicians are paid per patient recruited— generating a conflict of interest. Those recruited trust their physicians and willingly enroll so that they can access treatment and receive better care than otherwise available. They often sign the consent form without reading it, and reading it does not make a difference. Educated people and even some RECs have difficulties understanding the forms.

Studies have documented that CT subjects in Argentina, Costa Rica, Mexico and Peru were unaware that they were participating in clinical experimentation despite having signed the consent form. They were confused about their treatment, those in the placebo arm attributed 'side effects' to the drug, did not know who to contact when experiencing problems with their treatment and ignored that they were protected by an insurance policy[15].

The Peruvian RA interviewed subjects in three CTs and documented numerous examples of undue inducement. Subjects thought that they were in a program and not in an experiment and unaware of their rights and obligations. Patients signed the informed consent because they were promised a faster cure or a significant increase in their probability of recovery. Those who read the informed consent form failed to understand key words and concepts[15].

Poor understanding of the informed consent can compromise the quality of CT data and subjects' safety. In the Peruvian study, some patients self-medicated (including with herbal products) or used other health care providers without informing the CT implementation team. Health providers, ignoring that the patient was participating in a CT, might have failed to identify adverse events attributable to the experimental drug or could have prescribed additional medications exposing CT participants to drug-to-drug interactions[15].

5. Insufficient protocol information

The protocols do not include budgets and contracts, consequently RECs are unable to identify the conflicts of interest with PIs, site managers and subject recruiters[16].

Previous information about the product is, according to some authors, basic to decide if a protocol should be approved. Kimmelman and Federico[17] suggest that studies in humans should only begin after experts independent from the industry have analyzed the preclinical evidence and added: "RECs do not have the capability or resources to do such an evaluation".

CAN RECS BE HELD RESPONSIBLE FOR THE ETHICAL IMPLEMENTATION OF CT?

The RECs' capacity to evaluate CT sponsored by industry has not been formally assessed in LA. Available information and the limitations mentioned above indicate that approved protocols do not always comply with universally accepted ethical principles and do not protect subjects.

It will be unfair to blame RECs for their deficient performance. They have major structural constraints, lack needed resources and training, and if they discover violations they do not have enforcement powers. At most, they can inform the RAs. Not even all RAs have the capacity to sanction PIs or dare to stop a CT.

The existence of RECs makes everybody feel good, they protect subjects and block the use of risky medicines. The unpleasant truth is that they are doing none of the above. To say it in plain and frank terms, they are totally useless. The only thing they are responsible for is delaying drugs from entering the market.

WHY DO WE HAVE RECS?

Using President Trump's comment on the industry regarding drugs' high prices we could answer: "To let pharmaceutical industries to get away with murder".

When CTs subjects die or experience side effects or deviant/illegal/unethical behaviors are uncovered during CT implementation, the pharmaceutical industry is quick to point out that the CT had been approved, not by one, but by several RECs.

The industry has been extremely successful in controlling or neutralizing all forces that place obstacles to the maximization of their financial benefits. In the US, the industry is among the highest contributors to political campaigns[18], employs thousands of lobbyists[19], finances most patients' organizations[20], renders most scientific journals financially viable[21], pays for almost all continuous education courses for physicians[22], exercises considerable influence on all RAs[23], WHO[24], OECD, has strong ties with the US NIH, and controls the US clinical registry[8] www.clinicaltrials.gov.

Why should anyone doubt that the industry has an interest and uses all necessary means to control the implementation of CTs, which are the costlier component of pharmaceutical R&D?

The first to oppose the removal of RECs would be the pharmaceutical industry provided that they respond to its needs, that is, speedy approval of protocols with very few and minimal changes, and smooth CT implementation. The industry is successfully achieving these objectives. RECs protect sponsors from critics that raise ethical and human rights abuses occurring during the CTS. It can be said that the pharmaceutical industry needs the RECs.

WHAT CAN BE DONE?

It is naïve to present a proposal to overcome the power and resources of the pharmaceutical industry. Aware of this reality we advance a few ideas that we understand are radical, even if based on plain common sense. After about 30 years, it is undeniable that RECs are unable to fulfill their obligations and, albeit unwillingly, they are legitimizing the ethical and human rights violations perpetrated by industry. Any suggestions for improvement will be regarded as radical by those who prefer keep things as usual.

These are our ideas:

1. LA RECs should not be responsible for the scientific aspects of CT protocols. This role should be transferred to a few independent committees composed of national and international experts with no conflict of interests, able to consult with other independent specialists when needed. How protocols are assigned to these committees should not be determined by the pharmaceutical industry.

   These RECs would need to review all information on prior preclinical and clinical studies and on the pharmaceutical compounds to be tested. Independent pharmacology organizations could provide meaningful assistance on the organization and recruitment of members for these RECs, which should be appropriately resourced. How to define and insure independence in a field where billions of dollars are at stake needs to be studied, will not be easy, but it is essential.

   Similarly, some technical entity would have to establish the affordability thresholds of the new technologies, RECs are unable to do it.
2. The number of CTs being conducted is not aligned with the very few truly innovative drugs that are being commercialized, resulting in thousands of subjects being exposed to risks without any real scientific purpose, an obvious ethical and human rights violation. Independent experts need to explore why this is the case. Who will be willing to finance an independent commission to investigate it, remains a question mark. In LA, if our previous

comments were incorporated (no trials for unaffordable drugs, for placebo-controlled and inferiority trials, and a fair distribution of subjects by income levels) the number of CTs would be drastically reduced. There are many powerful stakeholders that welcome more rather less trials and will oppose this idea.

3. The key role of appropriately resourced institutional RECs should be limited to monitoring CTs. Their specific tasks and methods will need to be defined by experts but, among many others, they should approve the recruitment process, check the role of physician-recruiters, the economic stratum of subjects, and closely monitor adherence to the inclusion/exclusion criteria. The current tendency of recruiting among the poor needs to be reversed, except for CT of drugs for diseases that mostly affect them. In-depth interviews with subjects should be conducted.
4. Most subjects do not understand the consent form and solutions are not easy. It is unlikely that RECs can revise them. One solution would be to have specialized committees that translate the form to the literacy level of subjects. These committees do not need to include ethics experts. The ideal professional composition of these committees, who should appoint them, and funding mechanisms need to be studied. RECs, by interviewing subjects, will verify if the Consent Form Committee has achieved the objectives.
5. Since commercial RECs have unavoidable conflicts of interest, the current trend of promoting them should be reversed. It is anticipated that the industry will oppose the change.

After reading these paragraphs, it is obvious that the key word is independence. It is a pre-requisite for changes, whatever they are, to overcome the control that the pharmaceutical industry has of most stakeholders in this complex field. Changing the responsibilities of RECs and creating a variety of other committees could be an improvement, but their efficacy will be minimal if the decisions are not independent of the commercial interests of the industry, respect the human rights of subjects and focus in the advancement of medical science.

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Adaptación de los Comités Éticos de Investigación Clínica a las nuevas exigencias de la legislación vigente

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INTRODUCCIÓN

La ley 14/2007 de investigación biomédica, en su artículo 12, definió los Comités de Ética de la Investigación, determinando, en su disposición transitoria tercera, que los Comités Éticos de Investigación Clínica dejarían de existir en el momento en que se constituyeran los Comités de Ética de la Investigación.

El Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos, se publicó con objeto de desarrollar las disposiciones específicas para la aplicación en España del Reglamento (UE) n.º 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014, sobre los ensayos clínicos de medicamentos de uso humano. Este Real Decreto, a su vez, regula los Comités de Ética de la Investigación con medicamentos, de forma que establece los requisitos adicionales que deben cumplir los Comités de Ética de la Investigación para poder ser acreditados como Comités de Ética de la investigación con medicamentos (CEIm).

Recientemente la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) ha publicado el documento "*criterios específicos comunes para la acreditación, inspección y renovación de la acreditación de los CEIm*", consensuado entre las CCAA y la AEMPS y refrendado por el Comité Técnico de Inspección (CTI) con el fin de reforzar la transparencia y facilitar que las partes interesadas cumplan con la legislación aplicable. Este documento establece los criterios específicos comunes para la acreditación, inspección y renovación de la acreditación de los CEIm, complementarios a los requisitos de acreditación establecidos en el Real Decreto 1090/2015, de 4 de diciembre, y a aquellos que correspondieran para la acreditación como CEI en la Ley 14/2007, de 3 de julio, de Investigación biomédica y en su normativa de desarrollo. Este documento define, entre otros, cuestiones referentes a la composición, el funcionamiento o los medios que debe disponer la propia secretaría técnica de un CEIm.

OBJETIVOS

El objetivo de esta revisión es analizar cómo se han adaptado los Comités Éticos de Investigación Clínica en España a las exigencias del Real Decreto 1090/2015 y Ley 14/2007 de Investigación Biomédica.

MATERIAL Y MÉTODOS

Se elaboró un cuestionario diseñado para recoger información sobre recursos humanos y materiales y sobre funcionamiento de los Comités Éticos de Investigación Clínica. El documento se envió en febrero de 2017 a todos los Comités Ética de la Investigación, a través del portal SIC-CEIC de la AEMPS y a un comité de ámbito universitario. Se han analizado todos los cuestionarios cumplimentados recibidos hasta el 13 de marzo de 2017.

RESULTADOS

Información general sobre los Comités: aspectos estructurales

Se ha recibido un total de **40 cuestionarios cumplimentados** por diferentes Comités de Ética de la Investigación de España. De estos 40 Comités que respondieron a la encuesta remitida por la secretaría del CEIm de Euskadi, 25 describieron que eran CEIm, 9 CEIC, 4 CEI y 2 comités se definían como CEIm/CEIC (Fig. 1).

Entre los Comités que han actuado como CEIm en alguna ocasión el 58,6% (17/29) evaluó <10 ensayos clínicos, el 21,4% (6/29) entre 10-25 ensayos clínicos y el 20,7% (7/29) >25 ensayos clínicos (Fig. 2).

De los 40 comités que han participado en esta encuesta, el 72,5% (29/40) están adscritos o ubicados en un centro hospitalario; el 22,5% (9/40) eran autonómicos, regionales o provinciales; el 2,5% (1/40) pertenecía a una universidad y el 2,5% restante (1/40) a un Organismo Público de Investigación (OPI).

De los 40 Comités encuestados 18 (45%) actúan como **CEI externo de un Biobanco**.

La mayoría de los cuestionarios han sido respondidos por los secretarios de los Comités (20), seguidos por los presidentes (8) y miembros de la secretaría técnica (7). El resto por vocales (2), presidentes/secretarios (2) y vicepresidente (1).

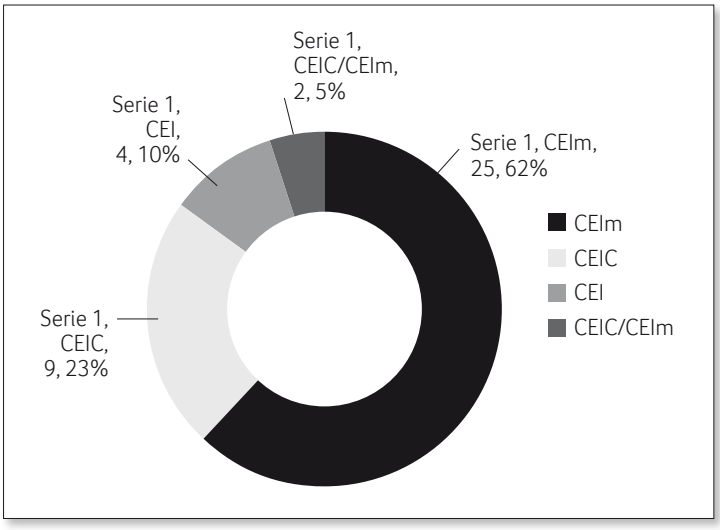

FIGURA 1. Clasificación por tipo de Comités que han respondido al cuestionario.

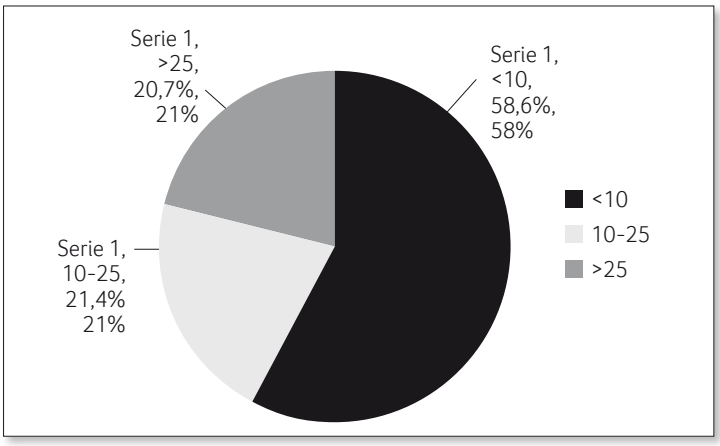

FIGURA 2. Porcentaje de comités en función del número de ensayos clínicos evaluados durante el 2016.

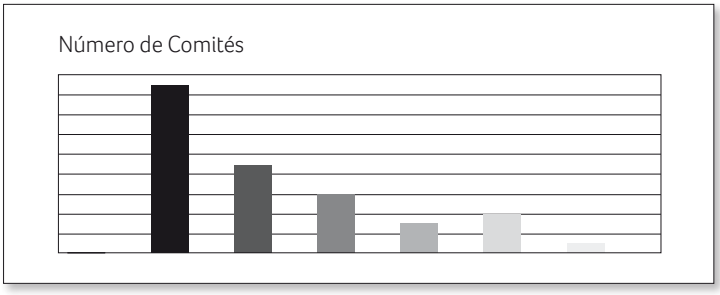

FIGURA 3. Número de Comités en función del número de miembros que forman parte de la secretaría técnica.

En cuanto a las **secretarías técnicas** de dichos comités, 17 (el 42,5%) están compuestas por un miembro, 9 (22,5%) por 2 miembros, 6 (15,0%) por 3 miembros, 3 (7,5%) por 4 y otros 4 (10%) por >4 miembros. Solo un comité respondió que no dispone de secretaría técnica.

En la mayoría de los casos (89%) la secretaría técnica está integrada en el organigrama de la institución a la que está adscrita.

El número total de miembros en cada comité varía desde 10 miembros en el comité con menor número hasta 27 en el comité con mayor número, siendo la mediana de 18 miembros.

Acerca de la **composición de los comités**, la mayoría tiene más de 4 médicos, tal y como respondió el 93% de los encuestados (37). Un comité respondió que en su composición contaba con 4 médicos. No hubo respuesta en 2 cuestionarios.

Aspectos relacionados con el procedimiento de acreditación del CEIC/CEI/CEIm

En el 75% de los comités encuestados existe un **procedimiento que garantiza la independencia** de los miembros del comité.

Los procedimientos utilizados varían desde:

- Compromiso personal de cada uno de los miembros con una declaración formal de ausencia de conflicto de interés y de confidencialidad: en 17 comités.
- Independencia garantizada por la composición del Comité: 6 comités.

- Procedimiento que exige que si algún miembro del comité está implicado en el estudio a evaluar o forma parte del equipo investigador deba abandonar la reunión y no participe en la discusión ni en la votación (respuesta de 4 comités).

Los **procedimientos utilizados para la renovación de miembros** son diversos. A continuación se indican los reflejados en los cuestionarios cumplimentados por los comités:

En referencia a la pregunta de **cómo** se procede a renovar la composición las respuestas fueron las siguientes:

- Convocatoria pública y valoración de los méritos a través del CV (9).
- A demanda, no hay procedimiento establecido (6).
- La Comunidad Autónoma establece el procedimiento (4).
- A propuesta por parte de la Dirección/Presidente (5).
- Por invitación (3).
- A petición del miembro saliente (2).
- Idoneidad para las necesidades del comité e interés del candidato (3).
- Solicitud a la autoridad sanitaria correspondiente (1).
- Solicitud de miembros externos y renovación teniendo en cuenta la especialidad (1).
- Al tener ámbito regional se solicita a los demás comités acreditados en la región que propongan de 1 a 3 nuevos miembros (1).

En referencia a la pregunta de **cuándo** se procede a renovar la composición las respuestas fueron las siguientes:

- Tras una baja (6).
- Tras una ausencia injustificada de 3 o más reuniones consecutivas o de más de 6 en un año, incumplimiento reiterado de los procedimientos normalizados de trabajo, dejar de trabajar en el centro o por la aparición de conflicto de intereses (1).
- Por renuncia expresa o decisión del Comité con mayoría de 2/3 de los miembros, pero sin perder la experiencia (1).
- Cada 3 años se propone una renovación de un mínimo del 10% y máximo del 50% de los miembros (1).
- Cada cuatro años se procede a la renovación de un tercio de los miembros (1).
- Por bajas espontáneas o con cada reacreditación se renueva al menos el 10% de los miembros (1).
- Cuando se cumple el plazo de reacreditación (1).
- Tras cada período de acreditación de 3 años se renueva prácticamente la mitad de los componentes (1).

En cuanto a la **sustitución** de miembros, cuando uno de ellos solicita la baja en el Comité, en 14 de los comités no existe un procedimiento específico como tal. Los métodos utilizados son los siguientes:

- No hay procedimiento especifico (14).
- Invitación directa o propuesta del Comité (9).
- Publicación de convocatoria (8).
- Se sustituye por otra persona de perfil similar (7).
- El miembro saliente propone un sustituto (6).
- Contacta de manera informal con servicios clínicos de interés (2).

- Candidatos que hayan mostrado previamente su interés (2).
- A propuesta de la Dirección del centro (1).
- Se pregunta voluntariamente y se valora (1).
- A propuesta del presidente en caso de tratarse de miembros imprescindibles, si no se considera necesario no se sustituye (1).
- Se presenta la baja ante el Programa de Ensayos Clínicos con Medicamentos de la Comunidad Valenciana, que es quién establece los requisitos (1).

En los comités donde no hay un procedimiento específico se utilizan diferentes métodos, en función de las circunstancias y necesidades.

Solo en el 10% de los comités (4) es el miembro saliente el que propone un sustituto y en el 30% (12) se ha procedido de esta manera en alguna ocasión, pero no se utiliza este procedimiento como norma general.

Respecto al **procedimiento adoptado cuando se incorporan nuevos miembros** al comité, casi la mitad de los encuestados, 48% dispone de un procedimiento específico. Entre los procedimientos especificados se describen:

- Convocatoria pública (6).
- A propuesta del presidente u otro miembro del comité (4).
- A propuesta del Gerente del Departamento (1).
- Mediante entrevista: se informa sobre los procedimientos del comité, se le facilita un dossier con documentos claves para la evaluación ética-legal, reglamentos,...Durante un mes no se le asignan proyectos específicos para evaluar y acompaña a los ponentes (1).
- Las nuevas incorporaciones participan en el CEI un mínimo de tres meses, sin realizar funciones de evaluación, coincidiendo con los miembros salientes, con objeto de que conozcan el procedimiento de trabajo y se integren adecuadamente en el comité (1).
- En el PNT específico sobre sustitución y renovación se especifica que existe la posibilidad de nombramiento de miembros de libre designación para garantizar en todo momento que la composición del comité cumple con lo establecido en la legislación. Los componentes que representan a otro comité acreditado en la región son la mayoría de los miembros (1).
- Se exige que sea un profesional que disponga ya de conocimientos, además de cumplir con los requisitos, autorización de la gerencia y voluntariedad (1).

En relación a las cuestiones referentes al **asesoramiento por personas expertas** ajenas al Comité en la evaluación de algún ensayo, el 60% (24) de los comités encuestados ha solicitado este asesoramiento. Solo en el 50% (20) de los comités existe un procedimiento específico para solicitar el asesoramiento por parte estos expertos (Fig. 4).

En el 20% (8) de los comités encuestados estos expertos externos reciben dietas por prestar asesoramiento y/o asistir a las reuniones del comité. En un comité se les paga los gastos del viaje para asistir a las reuniones.

En cuanto al **pago de dietas**, en el 23% de los comités se paga a los vocales en concepto de asistencia a las reuniones; en un comité solo se paga cuando las reuniones son por la tarde, en otros dos casos solo a los miembros externos y en un caso únicamente se paga el desplazamiento a que vienen de otra ciudad.

En referencia a si se reconoce la carrera profesional de los miembros del comité, únicamente en el 40% (16) la respuesta fue afirmativa, aunque hubo un 8% (3 casos) en los que

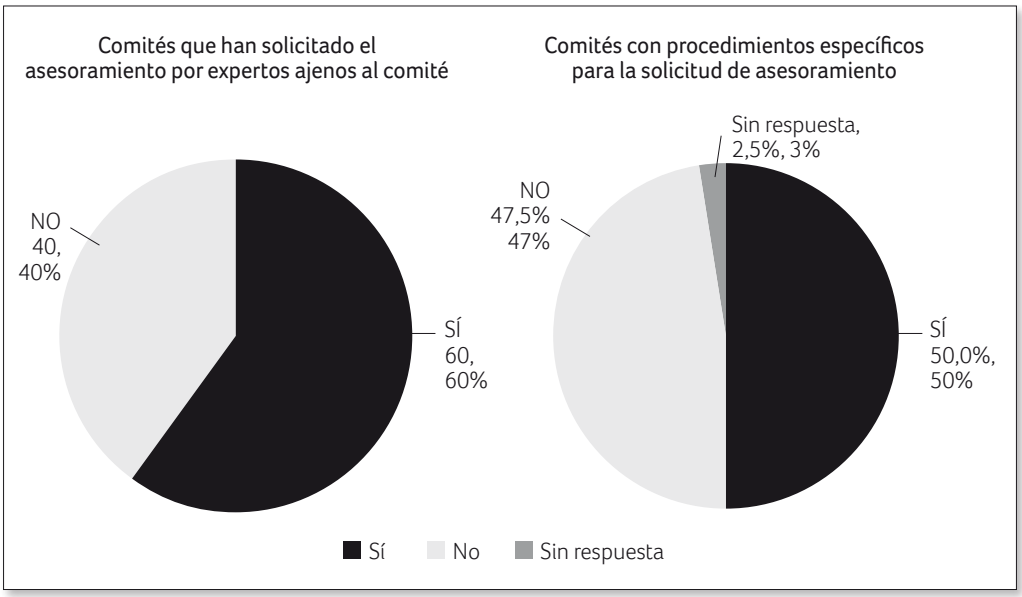

FIGURA 4. Clasificación de los comités en función de si han solicitado asesoramiento a expertos externos al comité y si disponen de procedimiento específico para ello.

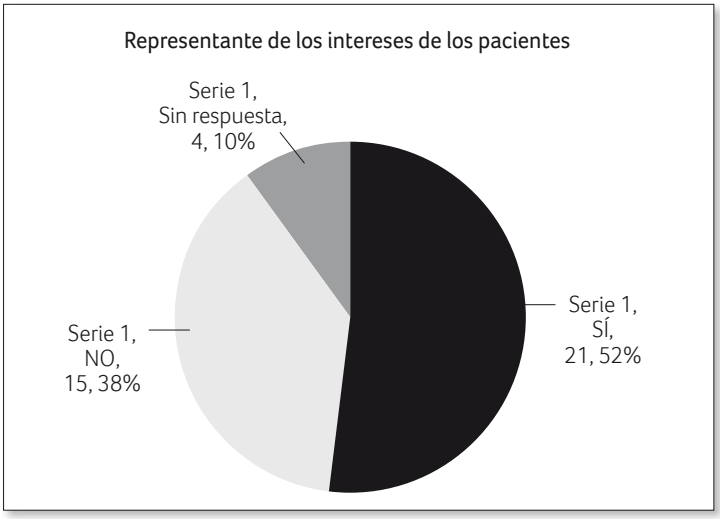

FIGURA 5. Número de comités que han incluido un representante de los intereses de los pacientes.

se desconocía la respuesta. De estos 16 comités prácticamente en todos (13) se tiene en cuenta el tiempo de participación para la misma.

Sobre la inclusión de un **representante de los intereses de los pacientes** en el comité, solo en el 52% (21) de los casos han incluido esta figura, aunque en esta pregunta hubo un 10% (4) de Comités que no respondieron (Fig. 5).

Los procedimientos utilizados para la selección de estos miembros fueron diversos:

– Por invitación directa (4).

- Por parte de la Consejería, previo contacto con las organizaciones de pacientes (1).
- Convocatoria abierta y evaluación de méritos (1).
- Representante de las organizaciones de consumidores y usuarios (1).
- A propuesta de la autoridad sanitaria competente (1).
- A través de trabajadores sociales se han entrevistado diversos candidatos que han mostrado interés (1).
- Un miembro de la Unidad de Atención al Paciente y un miembro ajeno a las profesiones sanitarias. Se está trabajando para que el miembro ajeno sea representante de una asociación de enfermos (1).
- Una persona de atención al usuario (1).
- A propuesta de una organización/asociación de pacientes. En un comité respondieron que se selecciona un representante de la asociación del colectivo de pacientes que más EECC evalúa. En otro comité se elige un paciente de la asociación con mayor peso específico y mayor número de socios (1).
- Propuesto por la Presidenta del comité y elegido entre los pacientes que acudan a las consultas de un servicio y que posean un perfil adecuado (1).

Solo en el 15% (6) de los comités están representados los centros privados; en cambio, el 83% (33) de los comités tiene representación de profesionales de atención primaria en su composición.

Finalmente, el 38% (15) de los comités tiene establecido un tiempo máximo de pertenencia a los mismos. De estos no todos han indicado la duración del mismo. Entre los que sí la tienen preestablecida hay diferencias importantes que se detallan a continuación:

- 4 años (7).
- 6 años (4).
- 12 años (1).
- No debe ser superior a cuatro períodos de acreditación consecutivos (1).
- El establecido por la legislación autonómica (1).

En 9 comités indicaron que existen excepciones o que se podría renovar o prorrogar este período para poder garantizar el correcto funcionamiento del comité.

Funcionamiento de los comités

En el cuestionario también se consultó sobre distintos aspectos relacionados con el funcionamiento de los Comités:

Solo el 25% (10) de los comités afirmó realizar reuniones no presenciales, siendo la multiconferencia telefónica el método más utilizado, por el 50% de ellos (5). El siguiente método más utilizado es la videoconferencia, en el 40% (4) de los comités que realizan reuniones no presenciales. Otro de los métodos utilizados citados es el email (1) (Fig. 6).

Respecto a cómo se garantiza el quórum en las reuniones no presenciales las respuestas fueron las siguientes:

- El mismo método que en las presenciales (3).
- Se exige confirmación de asistencia (3).
- Dos comités respondieron que se deja constancia, en el acta de la reunión, de los miembros que han acudido.
- Siempre hay quórum (1).

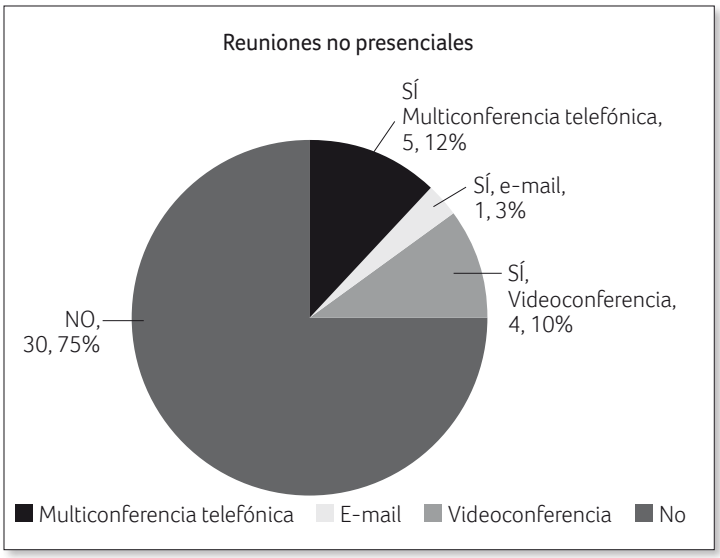

FIGURA 6. Porcentajes de comités que realizan reuniones no presenciales.

– Solo se ha utilizado la posibilidad de reuniones no presenciales en dos reuniones de verano, con un máximo de 2 personas en teleconferencia. El quórum ha estado garantizado en un 99% por asistentes presenciales (1).
– Por la participación de mayoría simple (1).

En el 70% (28) de los comités encuestados se cobran tasas por la evaluación de estudios, pero solo en el 44% (12) de ellos esta tasa revierte en la financiación de recursos del comité.

En cambio, cuando se pregunta por la gestión de los contratos, solo en el 60% (23) se contempla el pago de tasas (en uno de ellos únicamente cuando actúan como CEIm) pero únicamente en el 29% (7) revierte en la financiación de recursos del comité. En relación a esta cuestión se debe mencionar que en el 15% (6) de los comités encuestados esta cuestión no aplica, ya que especificaron que no es el propio comité el que se encarga de la gestión del contrato.

Por otro lado, se consultó sobre sistemas de gestión de calidad: el 25% (10) de los comités encuestados refieren tener implantado algún sistema de gestión de calidad. De estos comités 5 tienen instaurados Procedimientos Normalizados de Trabajo (PNT), 2 comités disponen de Certificación ISO, un comité UNE166.002:2014, en otros dos casos no se ha especificado.

En cuanto al seguimiento de estudios aprobados por los comités, el 43% (17) de los comités dedica una parte de la reunión al seguimiento (aunque en uno de estos comités solo ocasionalmente) y el 10% (4) contempla la realización de reuniones dedicadas exclusivamente al seguimiento de estos estudios.

LIMITACIONES

El escaso número de respuestas recibidas (32% de las enviadas) y la no cumplimentación del cuestionario completo en algunas ocasiones.

CONCLUSIONES

Tal y como se analiza en las respuestas de los comités encuestados se ha realizado un esfuerzo importante de adaptación a las nuevas exigencias de composición y funcionamiento establecidas por el Real Decreto 1090/2015.

La mayoría de los CEIC han asumido las funciones de CEIm mediante la adhesión al Memorando de Colaboración e Intercambio de Información entre la Agencia Española de Medicamentos y Productos Sanitarios y los Comités de Ética de la Investigación con medicamentos. En este sentido y en relación a la actuación como CEIm, valorando el número de ensayos clínicos evaluados, la mayoría de los comités ha evaluado menos de 10 ensayos clínicos al año. Esto coincide con los datos aportados por la AEMPS en la reunión del grupo de coordinación de EC de febrero, en la que se aprecia cómo el 66% de los comités que han evaluado durante el 2016 algún ensayo clínico, han evaluado <10, el 13% entre 10-25 y el 22% más de 22 ensayos clínicos.

Respecto a las exigencias de composición del Real Decreto 1090/2015 no todos los comités han incluido en su composición un representante de los intereses de los pacientes. Por otro lado, en referencia al funcionamiento, podemos destacar que es escaso el porcentaje de comités que realiza reuniones no presenciales. Además, no todos los comités disponen de un procedimiento específico para solicitar el asesoramiento por parte de expertos ajenos al comité.

Como tareas pendientes es destacable la necesidad de implantar un sistema de gestión de calidad en todos los comités, dedicar más recursos al seguimiento de los estudios aprobados y garantizar que las tasas reviertan, al menos en un porcentaje, en la financiación de los recursos de los comités, cuestión fundamental para garantizar la independencia y autonomía de los mismos. Asimismo, existe una necesidad de garantizar un método de trasparencia en la renovación de los miembros.

A la espera de conocer las exigencias de composición y funcionamiento de los Comités de Ética de la Investigación, en cumplimiento de la Ley 14/2007 de Investigación Biomédica, los comités han realizado un gran esfuerzo de adaptación a la exigencias adicionales del Real Decreto 1090/2015. Sin embargo, aún queda un largo camino por recorrer hasta la acreditación de los comités siguiendo las nuevas directrices publicadas, para lo que puede ser de gran ayuda conocer la situación de partida y que aspectos deben ser mejorados.

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Post-trial provision of investigational drugs: an ethical imperative for Research Ethics Committees

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ABSTRACT

The World Medical Association (WMA)'s Declaration of Helsinki outlining ethical principles for medical research involving human subjects includes a paragraph (no. 34) on the obligation of sponsors to make provisions for post-trial access to interventions "identified as beneficial" to research participants. Likewise, the Council for International Organizations of Medical Sciences (CIOMS) guidelines state that research participants should be informed about the extent to which "they will be able to receive beneficial study interventions post-trial" and point out that research ethics committees have a task in determining whether the arrangements for continued care are adequate. It is not clear whether research ethics committees routinely evaluate post-trial access provisions within research protocols, and what criteria they employ when doing so. Studies indicate that pharmaceutical companies rarely make arrangements for post-trial access. When they do, companies usually set up open-label extension studies to continue the supply of drugs to research participants. The stated aim of an open-label extension study, however, is –or should be– scientific, not therapeutic in nature, and may conflict with the actual aim of the study, namely: the provision of 'continued access' to seemingly safe and effective drugs that are not yet approved for marketing and thus not yet available to patients through healthcare systems. Yet many countries have programs in place for 'compassionate use' of investigational drugs by patients who have exhausted standard treatment options, who cannot enroll in clinical trials (e.g. because there are no clinical trials in their geographical region, or because they meet the exclusion criteria of existing trials), and for whom, to the judgment of their treating physician, the benefits of trying the drug will outweigh the harms. Post-trial access could thus be provided through expanded access programs for specified patient groups or for individual patients (so-called 'named-patient' programs), which have an explicitly therapeutic aim and are clearly regulated. In some countries, such programs are fully funded by the health-care system, whereas in other countries, they are paid for by drug developers or by patients themselves. As the awareness of –and demand for– early access to investigational drugs seem to be growing among patients and their treating physicians, research ethics committees will need to take on with increased urgency their responsibility to assess arrangements for adequate post-trial access. This presentation explores the potential role of named-patient programs in post-trial

access, proposes a preliminary set of criteria for the evaluation of post-trial access provisions to be used by research ethics committees, and offers recommendations for the incorporation of post-trial access information in the informed consent process.

Independence of Research Ethics Committees. Meaning and implications

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ABSTRACT

The independence of Ethics Committees must be recognized as an unavoidable condition, which needs to be permanently defended and protected. As an organization, the main threats come specially form the sponsors, the researchers themselves and the institution where they belong. About that, the Committees and its members usually receive several pressures that put on risk its integrity, compromising the objectivity of the role they play, exposing it to legal repercussions which affect their decisions.

In this sense, the suitability and actualization of the members and an expedited and timely communication with the researchers, sponsors and people involved in the investigative process, constitute essential tools for the achievement of effective goals. The components of a Committee require to have a training that favors raise questions and rethinking decisions, manifesting them with conviction and clarity. Their proposals must constitute determinations and not be understood as mere suggestions or recommendations; they have a regulatory ethical and legal responsibility from its capacity to identify adverse events in the protocols and also demand an obligatory fulfillment.

It is then necessary to identify the origin of the challenges, dilemmas and problems that can expose and debilitate the constitution of the Committee. Maintain strengths, good practices and responsibilities will favor their social and academic role. This will allow to define meanings and will minimize possible barriers, sustaining their independence.

Concerning that, health institutions and universities that have Committees must explicitly expose an acknowledgment and offer administrative mechanisms, that can make easier to occupy a defined place, autonomous, clearly diffused and recognized through statutes.

The researchers, for its part, needs to recognize the role of the Committee and interact in a harmonic and dialogic way with their members, so that can resolve opportunely the observations and suggestions in their projects.

This suggests the need for a common language between them, the existence of a monitoring system and a unique national registry; the maintenance and actualization of processes of accreditation and setting standards that involves researchers, people involved and sponsors. Conditions that must be taken up by the networked Committees themselves and the State.

Through the independence of Scientist Ethics Committees, they reaffirm its purpose. As a consequence, they have a positive impact in their own development and permanence through time, generating a meaningful and essential condition.

Inclusión de personas que padecen enfermedad avanzada /cercanas al final de vida como sujetos de investigación científica. Problemas Éticos. Consentimiento Informado

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INTRODUCCIÓN

La investigación con sujetos que padecen enfermedades avanzadas y que se encuentran cercanos al final de la vida (que en adelante denominaremos sujetos "EOL", por la expresión en inglés *End of life*) representa un campo especialmente controversial en lo que a investigación clínica se refiere. Por un lado, despierta temores y resistencias aún dentro de los mismos profesionales del área y, por otro, representa un desafío pues se dirige a personas que suelen experimentar un alto nivel de sufrimiento físico, psicológico y espiritual.

¿Por qué no investigar con los sujetos EOL cuando ello puede contribuir al alivio de estas personas? Sin duda que tal objetivo requiere de investigadores entrenados específicamente y de protocolos exigentes en materia metodológica y ética, así como de Comités de Ética en Investigación (CEI) que puedan evaluar esos protocolos sin prejuicios y con conocimiento de las características de la población EOL.

Nuestro interés con este trabajo es contribuir a un mejoramiento de la tarea de los CEI para propiciar una intervención más adecuada a las características de dicha población. Luego de contextualizar la situación, nos focalizaremos particularmente en algunas de las dificultades que se presentan al momento de obtener el Consentimiento Informado con estos pacientes.

INVESTIGAR CON POBLACIÓN VULNERABLE EN EL FINAL DE LA VIDA (EOL)

Algunas definiciones: EOL y vulnerabilidad

La Sociedad Española de Cuidados Paliativos señala que los criterios que permiten incluir a un paciente en la categoría EOL[1] son:

- Padecer una enfermedad avanzada, progresiva, incurable.
- Ausencia de posibilidades razonables de respuesta a un tratamiento curativo específico.
- Presentar síntomas intensos, múltiples, multifactoriales y cambiantes.

- Presentar gran impacto emocional –al igual que su familia– relacionado con la presencia, explícita o no, de la muerte cercana.
- Presentar un pronóstico de vida estimado inferior a 6 meses.

Los pacientes pueden ser oncológicos, no oncológicos, así como también pacientes que estén recibiendo cuidados paliativos[2]. En EE.UU, *Medicare* utiliza criterios semejantes para dar cobertura en el sistema *hospice*[3]. Ellos son:

- La enfermedad del paciente limita su expectativa de vida (dato que tanto él como la familia conocen).
- Paciente y/o familia han optado por el objetivo terapéutico de alivio sintomático y no de curación.
- El paciente presenta alguna de las siguientes características:
  - Progresión clínica de una enfermedad primaria documentada según los criterios de dicha enfermedad, con resultados de laboratorio, radiología u otros estudios.
  - Presencia de consultas al área de emergencias o internaciones hospitalarias en los últimos seis meses, o internación domiciliaria.
  - Empeoramiento del estado nutricional vinculado con su enfermedad.

Ahora bien, respecto de la noción de vulnerabilidad, tal condición puede manifestarse bajo distintas modalidades. Hay muchos criterios de clasificación al respecto. Consideraremos la llamada **vulnerabilidad intrínseca**, la que se asocia a factores como la edad (avanzada, geriatría o menores) o a la presencia de capacidades cognitivas reducidas por discapacidad o disturbios como la psicosis. La **extrínseca** se encuentra asociada a la presencia se situaciones externas limitantes tales como la hospitalización, la prisión o las limitaciones económicas. Finalmente, la **vulnerabilidad relacional** es aquella vinculada a la interacción con los cuidadores y que está determinada por la pérdida de independencia[4]. Los pacientes EOL con enfermedad avanzada son **vulnerables** en las tres dimensiones, la enfermedad los ha debilitado física y psicológicamente, a menudo se hallan hospitalizados y dependen del cuidado de otros[5,6]. Entendemos que la *vulnerabilidad* es un fenómeno complejo en el cual coexisten diferentes niveles y/o sectores de fragilidad interrelacionados y que experimentar vulnerabilidad en uno de ellos no necesariamente implica ser vulnerable en todos[7].

Por lo anterior, no debemos confundir **vulnerabilidad** con **no-voluntariedad** o con **incompetencia**. O sea que, si bien es cierto que hay que proteger a esta población de posibles situaciones de explotación, ello no autoriza a que se los despoje *per se* de sus capacidades como persona para transmitir o interrogar su sufrimiento, para contribuir o para sentir verdaderas intenciones altruistas[8].

Debates y problemas

Con lo antes expuesto surgen algunas preguntas referentes a los pacientes EOL. ¿Son un caso especial de sujeto de investigación? ¿Deben excluirse de cualquier investigación por ser pacientes murientes o por pertenecer a una población altamente vulnerable? ¿Pueden ser aceptables los resultados de investigaciones que tienen poblaciones tan heterogéneas, que presentan un alto índice de deserción de los sujetos, ya sea por fallecimiento o debido a que pierden capacidades y/o aptitud para permanecer en el estudio? ¿El diseño del estudio tiene que tener características particulares? ¿Cómo debería realizarse el balance riesgo-beneficio en estos casos? Y, particularmente ¿Cómo realizar el proceso de Consentimiento Informado?

Con tales interrogantes es fácil deducir que la investigación en el área de cuidados paliativos y/o con pacientes EOL es muy debatida y su implementación requiere conocimientos específicos[9,10]. Se podría decir que las mayores dificultades se vinculan con los siguientes factores:

- El medio y su modalidad de trabajo, donde se carece de la experiencia y el hábito de la investigación clínica.
- Las condiciones del paciente, con su gran debilidad física, la vulnerabilidad emocional y las alteraciones neuropsicológicas.
- La capacitación y la voluntad específica del personal sanitario.
- Las peculiaridades en la aplicación de la propia metodología de la investigación clínica en cuidados paliativos como, por ejemplo, la elevada pérdida de pacientes o la necesidad de herramientas específicas.
- Los límites éticos más evidentes de la investigación clínica, al referirse a pacientes especialmente vulnerables.
- La heterogeneidad de la población estudiada[11].

Algunos de estas dificultades son responsables muchas veces de que los CEI rechacen protocolos de investigación[12]. A ellas se suman la falta de comprensión y insuficiente conocimiento de la metodología adecuada para conducir una investigación en una población de estas características, la suposición de que hay que "prevenir investigaciones no-éticas" *a priori* del análisis del protocolo, la subestimación de los posibles beneficios para los sujetos que participan y la desestimación del posible interés de participar por parte de los mismos. Ciertamente la protección, fundamentalmente debido a una falta de educación específica sobre el área, termina en exclusión de los protocolos, privando a esas personas, pacientes EOL, del posible beneficio de un estudio que podría redundar en el alivio de sus síntomas y mejorar su calidad de vida.

OBTENCIÓN DEL CONSENTIMIENTO INFORMADO EN LA ETAPA EOL

El Consentimiento Informado (CI), su proceso de obtención, validez y legitimidad ocupan un lugar central en las preocupaciones bioéticas. En todo el mundo se busca consensuar regulaciones y, a la vez, cada país tiene su normativa específica[13].

Cuando se va a solicitar el CI a un paciente EOL, hay que tener en cuenta que, indudablemente, es un caso especial de sujeto de investigación y que detenta características únicas:

- Presenta multiplicidad de síntomas de diferente naturaleza y, por lo tanto para su atención, requiere de entrevistas profundas y extensas.
- Requiere de manera determinante que se pueda crear una conexión emocional y de confianza profesional- paciente- familia.
- Además, la información que circula durante las entrevistas suele contener elementos de pronóstico desfavorable o información acerca de la proximidad de la muerte o la no viabilidad de tratamiento curativo. Todo ello requiere tiempo para entender, para aceptar, para preguntar, para llorar...
- Paciente y familia experimentan una gran preocupación por la posibilidad de sufrimiento dada la presencia frecuente de síntomas devastadores tales como disnea, dolor y angustia existencial.

- Todo ello puede influir en crear expectativas no realistas acerca de la situación (a veces por demás positivas y otras excesivamente negativas)14 y más aún, si se le proponer ingresar a un protocolo en esa instancia.

En Argentina actualmente nos encontramos conduciendo varios protocolos de investigación cuyo propósito es documentar la eficacia de ciertas intervenciones en cuidados paliativos para lograr un mejor manejo de síntomas (especialmente dolor) en pacientes EOL con cáncer avanzado. En el desarrollo de esos, aparentemente simples, estudios observacionales y descriptivos, hemos encontrado importantes dificultades bioéticas, vinculadas especialmente con la obtención del CI.

Por un lado, debido al requerimiento de proveer la información apropiada, el CI demanda un gran número de páginas en su conformación. Necesario, lo sabemos, pero adquiere una extensión tal que excede la capacidad de comprensión y análisis que se requiere del/la paciente/ familia/ cuidador en ese estadio. Aclaremos que no es por la presencia de trastorno cognitivo, sino por el agobio propio de su enfermedad que lleva al paciente/familia a circunscribir su atención principal en sus síntomas, temores y en cómo aliviarlos.

Por otro lado, el CI requiere la inclusión de datos e información que pueden afectar las preferencias del paciente/ familia/ cuidador acerca de cuándo y cuánto desean conocer de su *diagnosis* y *prognosis*[15].

La primera entrevista de atención de su salud es frecuentemente el momento en que se genera la relación de confianza paciente/ profesional. Pero la primera entrevista es también el momento en que se debe invita al paciente participar en un protocolo y firmar el CI. Observamos que se produce así una disonancia entre el rol del "profesional-cuidador" de la salud y el rol del "investigador". Asimismo, los temores o aprensión acerca de los beneficios y las posibles desventajas de participar inevitablemente aparecen. En algunos casos, será posible separar el rol del investigador de aquel del profesional que lo atiende. Sin embargo, en la mayoría de los casos, ello no es factible ni funcional al protocolo, y suele ser el mismo profesional tratante quien, durante la primera entrevista, debe decidir si su paciente aplica o no a los criterios de inclusión y quien le propondrá ingresar al protocolo[16].

En este contexto es que nos preguntamos si es posible diseñar otro tipo de CI que sea más aplicable a la población EOL, que de ningún modo descuide sus derechos, pero que facilite de alguna manera su acercamiento a participar. Contribuiría también a que se desarrolle esta área que tanto bien puede hacerle ya que, efectivamente, muchas investigaciones con EOL arrojan resultados muy positivos en el corto plazo de los cuales el mismo sujeto podrá beneficiarse. Como un claro ejemplo de esto podemos mencionar un protocolo cuyo propósito fue investigar la factibilidad de reemplazar la vía endovenosa por la subcutánea en la medicación utilizada en el contexto de cuidados paliativos, y cuyos resultados tendrían un alto beneficio potencial para estos pacientes.

CONCLUSIONES

Las corrientes modernas de medicina y cuidados paliativos consideran que se debe permitir que los pacientes EOL ingresen a un protocolo, ya que rechazar su participación implica negar al sujeto un rol activo en vivir, prevenir y mejorar el cuidado propio y el de los

otros, así como detentar una concepción paternalista que sobreprotege al paciente y le quita derecho a decidir. Y, aunque es cierto que el enfermo ya soporta muchas cargas por su enfermedad, también tiene derecho a elegir participar siempre que la investigación pueda ofrecer beneficios para sí y para otros y posea mínimo riesgo de daño o carga.

El Dr. Eduardo Bruera señala que entre un 80 y un 90% de los pacientes atendidos en Cuidados Paliativos están en condiciones de participar de protocolos de investigación si son bien informados del propósito de la investigación y del potencial beneficio del estudio[17,18].

En tal sentido, sugerimos que al evaluar protocolos de investigación científica que involucren pacientes EOL, los CEI deberían considerar:

A nivel ético:

- La posibilidad de desarrollar alguna modalidad de CI más limitada o abreviada[19].
- Revisar la relevancia y extensión de la información requerida y la pertinencia de incluir o no expresiones como "*cáncer*", "*cuidado de fin de vida*" y "*muerte*". Una alternativa podría ser revisar los criterios de inclusión e incluir por ejemplo solo a aquellos sujetos que sí conocen su diagnóstico y pronóstico.
- Realizar un balance riesgo/ beneficio singular, considerando que los parámetros cambian rápida y significativamente en los pacientes que se hallan cercanos a morir[20,21].

A nivel metodológico:

- La recomendación de no incluir a esta población en protocolos de primera línea, donde el momento de establecer el vínculo coincida con el de plantear su inclusión en los mismos
- La recomendación de no incluir a esta población en protocolos a largo plazo, o que requieren muestras muy amplias[22].

A nivel científico:

- Que el equipo de investigación sea interdisciplinario, de preferencia entrenado en Cuidados Paliativos, considerando la complejidad multidimensional de los temas a abordar en esta etapa de la vida.

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que se trata de un fenómeno flexible y que presenta alternativas variables, que hay aspectos de esa vulnerabilidad que pueden ser removidos en capas y que no debe concebirse como una "masa sólida".

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Reflexiones sobre representación legal de los menores*

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LA PARTICIPACIÓN DE LOS MENORES EN LA INVESTIGACIÓN BIOMÉDICA

Uno de los aspectos más controvertidos de la participación de los menores de edad en investigación es el que se refiere a la emisión del consentimiento informado por los representantes legales de los mismos. En esta comunicación intentamos aportar elementos legales y éticos para la deliberación y decisión que deben adoptar los Comités de Éticas en estos casos.

OPINIÓN, CONSENTIMIENTO Y MADUREZ DEL MENOR

Tanto la legislación europea como la española han introducido progresivamente el principio de participación del menor en la emisión del consentimiento de manera adaptada a su edad. Así lo hacen el Convenio de Derechos Humanos y Biomedicina (art. 6); Reglamento (UE) 536/2014, de 16 de abril de 2014, sobre ensayos clínicos de medicamentos de uso humano (art. 32.2); el artículo 9.3 c) de la Ley 41/2002, de Autonomía del Paciente se remite a la Ley Orgánica de Protección Jurídica del Menor que, en su artículo 9, establece que para valorar la madurez del menor se pueden adoptar determinadas medidas pero que, en todo caso, en España, la legislación viene considerando que tiene madurez el menor de 12 años o más para que pueda expresar su opinión, siempre que no tenga modificada su capacidad, permanente o temporalmente.

*Esta Comunicación se inserta en la investigación realizada en el Proyecto I+D+i (Refª DER 2013-47232-R): "*Minority of age, vulnerability and biomedical research* y su contenido forma parte también del Informe presentado al Comité de Ética de la Investigación, del Instituto de Salud Carlos III, con el título *"Reflexiones sobre la participación de menores de edad en procesos de investigación y ensayos clínicos"*. Agradecemos a los miembros del Comité sus comentarios que enriquecieron el texto.

Las reglas generales de representación de los menores y de derechos y deberes de estos, se encuentran recogidas y reguladas en el *Código Civil* y son aplicables directa o supletoriamente, según los casos. El principio general es el de que los menores están bajo la patria potestad de los progenitores (o, en su defecto, sus representantes legales) y que la patria potestad obliga, entre otros aspectos, a **representarlos** y, si tuvieran suficiente madurez, a **oírlos** siempre antes de adoptar decisiones que les afecten (art. 154). El Código Civil no establece una edad determinada como criterio de madurez.

Por su parte la *Ley 41/2002 de autonomía del paciente* establece que debe obtenerse el consentimiento por "representación" de los padres o representantes legales cuando el menor de edad "no sea capaz intelectual ni emocionalmente de comprender el alcance de la intervención". La Ley dice que, en estos casos, se oirá al menor conforme a lo establecido en el artículo 9 de la Ley Orgánica 1/1996, de 15 de enero, de Protección Jurídica del Menor (Nueva redacción por L.O. 8/2015, de 22 de julio, de modificación del sistema de protección a la infancia y a la adolescencia), que establece que estas garantías son las siguientes:

- El menor tiene derecho a ser oído y escuchado sin discriminación alguna por edad, discapacidad o cualquier otra circunstancia,... Para ello, el menor deberá recibir la información que le permita el ejercicio de este derecho en un lenguaje comprensible, en formatos accesibles y adaptados a sus circunstancias.
- Se garantizará que el menor, cuando tenga suficiente madurez, pueda ejercitar este derecho por sí mismo (verbal o por otros medios) o a través de la persona que designe para que le represente. La madurez habrá de valorarse por personal especializado, teniendo en cuenta tanto el desarrollo evolutivo del menor como su capacidad para comprender y evaluar el asunto concreto a tratar en cada caso. Se considera, en todo caso, que tiene suficiente madurez cuando tenga **doce años cumplidos**.

La Ley 41/2002, de autonomía del paciente también establece que cuando se trate de menores emancipados o mayores de 16 años, que no tengan la capacidad modificada judicialmente y así conste en sentencia o no sean capaces intelectual ni emocionalmente de comprender el alcance de la intervención, no cabe prestar el consentimiento por representación, de donde se deduce que, en el ámbito de aplicación de la Ley 41/2002, el menor prestaría su consentimiento **directa y plenamente**, salvo las excepciones establecidas en la propia ley, ensayos clínicos y técnicas de reproducción asistida (art. 9.5).

Se excepciona también el consentimiento **directo y único** del menor cuando se trate de una actuación de grave riesgo para la vida o salud del menor, a criterio del facultativo (se trata, pues de pacientes menores de edad), en cuyo caso lo prestará el representante legal del menor, **una vez oída y tenida en cuenta** la opinión del mismo.

Por su parte, el artículo 4 de la Ley de Investigación Biomédica no alude a "tramos" de edad y solo autoriza la investigación "cuando no existan otras alternativas para la investigación". Si finalmente, hay investigación con menores, se establece que participarán en la medida de lo posible y según su edad y capacidades en la toma de decisiones a lo largo del proceso de investigación. La regulación de la LIB debería ser aplicable de manera prioritaria por cuanto es Ley especial sobre la más general Ley 41/2002 y en ausencia de una regulación más restrictiva en el Código Civil pero la regulación de la obtención del consentimiento es tan abierta que precisa del apoyo de otras normas éticas y legales.

La conclusión derivada de estas exigencias legales y éticas es que no debería evaluarse positivamente ninguna investigación en la que no se garantizara que no se llevará a cabo contra la opinión del menor, expresada formal o materialmente. Igualmente, la evaluación ética, debería tomar en consideración la edad de los menores y solicitar una explicación científica a la necesidad inexcusable de que participen en la investigación.

DERECHOS Y OBLIGACIONES DE LOS PADRES O REPRESENTANTES LEGALES EN LA EMISIÓN DEL CONSENTIMIENTO

En este aspecto, es relevante conocer si los padres deben o no prestar su consentimiento conjuntamente o si es suficiente con el consentimiento de uno de ellos y en qué casos.

El Código Civil establece que "la patria potestad se ejercerá conjuntamente por ambos progenitores o por uno solo con el consentimiento expreso o tácito del otro. Serán válidos los actos que realice uno de ellos conforme al uso social y a las circunstancias o en situaciones de urgente necesidad". Lo primero que debemos señalar es que la participación en una investigación no puede considerarse un acto dentro del "uso social" y difícilmente se dará también un caso de "urgente necesidad", por lo que, salvo excepciones, no procede que uno de los progenitores consienta en nombre de los dos.

Los padres que ostenten la patria potestad tienen la *representación legal* de sus hijos menores no emancipados, pero quedan exceptuados de esta regla: los actos relativos a los derechos de la personalidad que el hijo, de acuerdo con su madurez, pueda ejercitar por sí mismo; aunque los progenitores intervendrán en estos casos en virtud de sus deberes de cuidado y asistencia.

Por tanto, en relación con la participación en la investigación (que afecta claramente a la esfera de los derechos de la personalidad por afectar al derecho a la vida y a la integridad física) el menor tiene capacidad de consentir o no, en razón de su madurez (art. 162 CC.).

Sin perjuicio de lo anterior y a efectos de articular un procedimiento de evaluación de la investigación que, respetando las garantías legales y éticas, sea ágil, cabría establecer una regla para la emisión del consentimiento de ambos progenitores que permitiera que solo uno de ellos firmara el consentimiento siempre que el otro progenitor hubiera recibido la información previa y manifestado fehacientemente aceptar este procedimiento. Esta posibilidad encuentra fundamento, aun indirecto, en artículo 5.3 del Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos, establece literalmente que "Será necesario que se haya obtenido el consentimiento informado previo de los padres que no estuvieran privados de la patria potestad o del representante legal del menor, a quien deberá oírse si, siendo menor de doce años, tuviera suficiente juicio. *El documento de consentimiento informado de los padres será válido siempre que vaya firmado por uno de ellos con el consentimiento expreso o tácito del otro que debe quedar suficientemente documentado, según lo dispuesto en el artículo 156 del Código Civil.* Cuando las condiciones del sujeto lo permitan y, en todo caso, cuando el menor tenga doce o más años, deberá prestar además su consentimiento para participar en el ensayo".

En el párrafo anterior hemos hablado de *fundamento indirecto* y ello es posible en la medida en la que el Real Decreto 1090/2015, de 4 de diciembre, se aplica específicamente y

exclusivamente a ensayos clínicos con medicamentos y, por tanto, no sería aplicable a otras investigaciones de distinta naturaleza, tanto más, cuando podría interpretarse como una disminución de las garantías establecidas para estas últimas. Los ensayos con medicamentos pueden justificarse mejor en razón de la necesidad de obtener tratamientos eficaces, específicamente para patologías *en* menores o *de* menores, y por ello podría estar justificada esta norma en relación con el consentimiento de los padres. En una investigación que no tuviera la incidencia de un ensayo clínico con medicamentos, tal disminución de la garantía sería más discutible y requeriría una mayor explicación.

En todo caso, si se aplicara esta norma (participación directa de un progenitor con constancia del acuerdo del otro progenitor) en la evaluación de investigaciones que no fueran ensayos con medicamentos, el investigador debería siempre solicitar un documento expreso del cónyuge que no otorga directamente el consentimiento lo cual permitiría al Comité, en su caso, evaluar si se acredita suficientemente el consenso de ambos progenitores sobre la participación del menor en la investigación.

Creemos que en ningún caso debería aceptarse el denominado consentimiento "tácito" al que alude en el artículo 5.3 (incurriendo en notoria incongruencia), toda vez que si el consentimiento es "tácito" (es decir, se deduce, por no constar oposición manifiesta) no habrá, en ningún caso, un "documento" que lo justifique, pues de haberlo, ya no sería consentimiento "tácito" sino "expreso". Por otro lado, el artículo 156 CC al que se alude en el art. 5.3 no menciona la exigencia de "documentar" el consentimiento táctico ni el expreso.

DISCREPANCIA ENTRE LA OPINIÓN DEL MENOR Y DE LOS PADRES O DESACUERDO ENTRE ESTOS

Si los padres están en desacuerdo en relación con otorgar o no el consentimiento para la investigación, cualquiera de los dos progenitores podrá acudir al Juez, quien, después de oír a ambos y al hijo si tuviera suficiente madurez y, en todo caso, si fuera mayor de doce años, atribuirá la facultad de decidir al padre o a la madre. Si los desacuerdos fueran reiterados o concurriera cualquier otra causa que entorpezca gravemente el ejercicio de la patria potestad, podrá atribuirla total o parcialmente a uno de los padres o distribuir entre ellos sus funciones. Esta medida tendrá vigencia durante el plazo que se fije, que no podrá nunca exceder de dos años.

Lo anterior se aplica si los padres no están separados, ya que si es así, habrá que atender a quién tenga, en cada caso, la patria potestad. El artículo 156 del Código Civil establece que si los padres viven separados, la patria potestad se ejercerá por aquel con quien el hijo conviva. Sin embargo, el Juez, a solicitud fundada del otro progenitor, podrá, *en interés del hijo*, atribuir al solicitante la patria potestad para que la ejerza conjuntamente con el otro progenitor o distribuir entre el padre y la madre las funciones inherentes a su ejercicio. Igualmente habrá que atender al supuesto de que la patria potestad la tenga solo uno de los progenitores porque así se haya establecido por sentencia firme de conformidad con el artículo 170 del Código Civil o se haya producido alguna de las causas de extinción de la patria potestad que se señalan en el artículo 169 del mismo Código (una de ellas es la emancipación). Todo lo cual, en el ámbito de la obtención del consentimiento, obligaría a

conocer la situación de los padres en relación con la patria potestad y, por ello, su capacidad para otorgar o no el consentimiento conjunto o individual.

En relación con la obtención del consentimiento debe atenderse también al posible conflicto de intereses. Según dispone el Código Civil, siempre que en algún asunto el padre y la madre tengan un interés opuesto al de sus hijos no emancipados, se nombrará a estos un *defensor* que los represente en juicio y fuera de él. Se procederá también a este nombramiento cuando los padres tengan un interés opuesto al del hijo menor emancipado cuya capacidad deban completar. Si el conflicto de intereses existiera solo con uno de los progenitores, corresponde al otro por Ley y sin necesidad de especial nombramiento representar al menor o completar su capacidad (art. 163 CC.).

El menor emancipado actuará directamente y podrá emitir su propio consentimiento informado (art. 323 CC.). Dado que pueden acceder a la emancipación los menores que tengan 16 años cumplidos, esta previsión nos reconduce a la fórmula acogida, entre otras, en la Ley 41/2002, de autonomía del paciente que reconoce capacidad para otorgar el consentimiento directo, sin representación, a los mayores de 16 años.

La decisión del menor no prevalece sobre la de los padres de manera automática ni, bajo el punto de vista ético, debería prevalecer la de los padres sobre la manifestación de voluntad del menor (asentimiento). El asentimiento es una categoría ética que busca fundamentar la investigación en la cooperación voluntaria del menor previamente informado pero, como señalan las Pautas Éticas Internacionales para la Investigación Biomédica en seres humanos (Consejo de Organizaciones Internacionales de las Ciencias Médicas (CIOMS) en colaboración con la Organización Mundial de la Salud, 2002), tal "aceptación informada, algunas veces denominada *asentimiento,* es insuficiente para permitir la participación en investigación, a menos que sea complementada por la autorización de uno de los padres, un tutor legal u otro representante debidamente autorizado".

De otro lado, también la *oposición* del menor debe ser atendida en relación con su edad y madurez y en este principio hay acuerdo entre las normas éticas y jurídicas aunque el alcance de unas y otras sea diferente. Jurídicamente, si hay acuerdo entre los padres pero discrepancia con el menor o prevalecerá la opinión de los padres (lo cual encuentra apoyo en la legislación) o el asunto terminará judicializado y entonces la evaluación del Comité solo podrá ser, en su caso, una opinión técnica que será o no tomada en cuenta por el juez. Bajo el punto de vista ético, podría defenderse que la oposición del menor debería ser siempre dirimente, es decir, no debería autorizarse ninguna investigación en la que constara la oposición del menor, atendida siempre su edad y madurez pero esta posición ética entra en conflicto con la norma jurídica y no es recomendable que el Comité de Ética actúe en contradicción con dichas normas.

Así, pues, insistimos, el llamado *asentimiento* no permite autorizar una investigación a la que se opongan los progenitores pero una *oposición* del menor tampoco debería permitir dicha autorización. Conforme a esto, si hay discrepancia no puede autorizarse la investigación y habría que acudir, al juez. No siendo la investigación, por lo general, casos de riesgo vital, sería muy difícil que un juez autorizara la participación del menor que haya expresado su oposición. En todo caso, lo importante es que la evaluación ética no informe favorablemente ninguna investigación en la que no se confirme que habrá acuerdo entre la opinión del menor y la de los padres.

Es obvio, que pueden presentarse situaciones específicas en las que pudiera pensarse en la conveniencia de que el Comité de Ética prescindiera del consentimiento de los progeni-

tores como algunas investigaciones que implicaran información sensible sobre los menores (creencias, consumo de drogas, abusos, etc.). El documento CIOMS permite que en ciertos casos el Comité de Ética prescinda del consentimiento, sin embargo, la legislación española lo impide. En estos casos, como cuando hay discrepancia entre el menor y sus progenitores o entre estos entre sí, la única posibilidad es elevar el caso al juez, con intervención del Ministerio Fiscal, para que se determine lo que proceda. Si el Comité de Ética prescinde, aun con base ética suficiente, en la exigencia de que conste el consentimiento informado de quien deba prestarlo se arriesga a una respuesta judicial contundente si tal actuación no tiene el apoyo expreso de la norma jurídica.

Quizá, resulte de interés puntualizar el alcance de los términos *asentimiento* y *consentimiento*. Gramaticalmente, pueden utilizarse como sinónimos. Las Pautas Éticas Internacionales antes citadas, utilizan el término *asentimiento* como sinónimo de *acuerdo* del menor con sus progenitores o representantes en su participación en la investigación.

En el ámbito jurídico, sin embargo, se defiende cierta diferencia entre ellos. *Consentir* sería una manifestación de voluntad de aceptar, obligarse, no oponerse, a un hecho, un efecto jurídico, o una situación, en la que el que consiente es el sujeto activo en la relación. *Asentir* sería igualmente una manifestación de voluntad del sujeto pero posterior a una iniciativa ajena. Sin perjuicio de lo anterior, también se ha defendido que el término asentimiento representa una manifestación de voluntad de quien no está obligado (o capacitado) para consentir en términos jurídicos. Se pretende con ello usar un término diferente del usualmente utilizado por las normas jurídicas para designar la manifestación de voluntad de carácter obligatorio. En el contexto de la evaluación de una investigación con menores, el uso del término *asentimiento* sería válido para referirnos a la manifestación de voluntad de un menor que deba ser escuchado pero que no tenga atribuida por ley la capacidad para otorgar por sí mismo el consentimiento informado. Con todo, el uso del término *asentimiento* puede dar lugar a equívoco y solo debería utilizarse si el contexto permite una interpretación clara de la situación. Finalmente diremos que el término *asentimiento* no debe justificar la aparición de una categoría nueva de manifestación de voluntad que no haría sino confundir los derechos y obligaciones de las partes implicadas en estos casos. También debe insistirse en que el proyecto debe ofrecer garantías ciertas de que la participación del menor es inexcusable.

ACCESO DE LOS PADRES O REPRESENTANTE AL DESARROLLO DE LA INVESTIGACIÓN

Dado que los padres o representante del menor disponen de la capacidad de retirar al menor de la investigación en cualquier momento, sin necesidad de aportar ninguna explicación y sin recibir ningún tipo de represalia (si fuera el caso), puede defenderse, como ya se ha contemplado expresamente en algunos documentos éticos (por ejemplo, en las Pautas Éticas Internacionales, ya citadas), que debería reconocerse a los padres o representante la posibilidad de observar el desenvolvimiento de la investigación, en la parte en la que participara el menor, para permitirles tener elementos de juicio suficientes para, en su caso, tomar la decisión de retirar al menor de la investigación. Esta decisión forma parte del contenido de su derecho de representación del menor y de su obligación de velar por su superior interés.

¿Qué conocimiento tienen los investigadores sobre los principales documentos de ética en investigación? Resultados preliminares de una encuesta en un hospital universitario

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INTRODUCCIÓN

La investigación clínica es fundamental para introducir nuevos avances y tratamientos en la práctica médica que reducen la morbimortalidad y mejoran la calidad de vida de los pacientes. A pesar de estas evidentes aportaciones existen desde hace años ciertas reservas sobre cómo se realizan los estudios clínicos y cómo se protegen los derechos, la seguridad y el bienestar de los participantes.

Durante el pasado siglo, se publicaron documentos muy importantes que han ido definiendo con los años los principios de bioética que constituyen actualmente el marco de referencia de cualquier experimentación que se lleve a cabo en seres humanos, incluyendo aquellos estudios que se realizan con sus muestras biológicas y sus datos clínicos asociados. Algunos de ellos pueden considerarse como los más relevantes, ya que aparecen como hitos históricos en algunos momentos concretos a consecuencia de atrocidades como son el Código de Nüremberg (1947) y el Informe Belmont (1979), mientras que otros fundamentan su papel en el amplio consenso que existe sobre su relevancia, como son la Declaración de Helsinki (DoH, 1963) y la Guía del CIOMS (1982). Todos ellos constituyen las bases de la bioética de la investigación en humanos.

Tanto el Código de Nüremberg(1) como el Informe Belmont(2) vieron la luz tras hacerse públicos experimentos escandalosos con seres humanos. El código de Nüremberg fue publicado en 1947 tras el proceso judicial contra los responsables médicos de la experimentación nazi en campos de concentración/exterminio y es considerado el punto de partida y primera referencia de los códigos éticos en investigación médica. Algunas décadas más tarde, en los EE.UU., la Comisión Belmont redactó el informe del mismo nombre por encar-

*Miembros del CEI del Hospital Germans Trias i Pujol: Àngels Avecilla, Beatriu Bayés, Sandra Cabrera, Carmen Balañá, Cristina Casanovas, Natalia Dachary, Magí Farré, Àngels Fortes, Irene Jiménez, Ana María López, David López, Eva Montané, Albert Oriol, Jordi Peláez, Paloma Puyalto, Cristina Ramo, Joan Romeu, Mayka Sánchez, Montserrat Solà, Laia Vilaró.

go del congreso americano, en respuesta al polémico estudio Tuskegee (1979). El informe Belmont, además de articular una serie de principios éticos básicos que pudieran servir de guía para la experimentación en humanos, dio lugar a la creación de los primeros comités de ética institucionales.

Si hay un documento de referencia en el campo de la ética aplicada a la investigación biomédica, este es la Declaración de Helsinki (DoH)[3]. La DoH fue aprobada por la Asociación Médica Mundial en la capital finlandesa en 1964 y ha visto diferentes revisiones desde entonces, la última en 2013 en Fortaleza (Brasil). El cumplimiento de los principios de la DoH se recomienda en las guías de Buena Práctica Clínica de la Conferencia Internacional de Armonización[4]. En Europa, la legislación sobre ensayos clínicos[5] también se refiere a ella en su articulado, de manera que convierte en preceptivo su cumplimiento. Los médicos u otros profesionales que colaboran en ensayos clínicos con medicamentos como investigadores principales se comprometen a respetar sus principios en el momento en que firman el protocolo del ensayo.

De los cuatro documentos mencionados, la guía del *Council for International Organizations of Medical Sciences* (CIOMS, organización no gubernamental que colabora con la Organización Mundial de la Salud), es el más reciente y también es el más extenso. La primera versión fue publicada en 1982 y ha sido revisada en el año 2017. A diferencia del resto de documentos, redactados como una declaración de principios, contiene información detallada y ejemplos para facilitar a los investigadores su aplicación práctica[6].

Parece obvio que a cualquier profesional implicado en investigación en humanos, se le debería exigir un buen conocimiento de la DoH y, cuando menos, alguna noción del resto de los documentos de bioética antes mencionados, pero particularmente a aquellos que asumen el papel de investigadores principales en ensayos clínicos y que por lo tanto, se encuentran legalmente obligados. En el caso de los miembros integrantes de los Comités de Ética de la Investigación (CEI), que son los encargados de velar por la ética de los estudios en sus ámbitos de actuación, cabe suponerles también buenos fundamentos sobre estos y otros textos relevantes en esta materia. Sin embargo, en España, aunque la legislación vigente[7] exige que al menos uno de los miembros del CEI tenga formación acreditada en bioética (lo que permite asumir en su caso un sólido conocimiento de los mencionados documentos) no establece ningún requisito en este sentido para el resto de los integrantes.

No hay muchos estudios que hayan analizado el grado de conocimiento de los profesionales implicados en investigación sobre la DoH y el resto de documentos descritos. Los pocos estudios publicados son todos ellos encuestas realizadas a diferentes grupos de profesionales (en su mayoría médicos y enfermeros pero también a estudiantes de medicina, de odontología y otras profesiones sanitarias). Los resultados son variables pero indican que la mayoría de los encuestados no están familiarizados con la DoH, ni tampoco con el Código de Nüremberg o la guía CIOMS. Ninguno de los estudios identificados ha analizado el grado de conocimiento de los profesionales acerca del Informe Belmont[8-15].

En nuestro entorno tampoco disponemos de información precisa de hasta qué punto los profesionales relacionados con la investigación en seres humanos conocen estos documentos de referencia. Identificar posibles carencias en este aspecto debería conducir a

la implementación de acciones formativas dirigidas tanto a los profesionales implicados directamente en la investigación como a los miembros de los CEI.

OBJETIVOS

Describir el conocimiento que los investigadores y miembros del CEI del Hospital Universitari Germans Trias i Pujol (HUGTP) y de la Fundación de Investigación del Hospital tienen de cuatro de los principales documentos de ética en la investigación: el Código de Nüremberg, la Declaración de Helsinki, el Informe Belmont y la Guía del CIOMS.

MATERIAL Y MÉTODOS

Para los objetivos del estudio, se planteó llevar a cabo una encuesta dirigida a profesionales con experiencia como investigadores y/o miembros del CEI del Hospital Universitario Germans Trias i Pujol.

Se llevó a cabo una fase preliminar o piloto del trabajo, para la cual se construyó un cuestionario breve en formato impreso, que pudiera ser respondido de forma rápida y completamente anónima por los participantes. El cuestionario incluyó un total de 12 preguntas de elección múltiple, relativas a algunas características demográficas de los participantes, así como a su experiencia investigadora en los últimos 10 años, en proyectos promovidos por compañías farmacéuticas o en proyectos independientes, ya fuera como investigador principal o como colaborador. También se preguntaba sobre la experiencia (actual o en el pasado) como miembro de un CEI. Una de las preguntas iba dirigida a sondear si el participante había recibido en los últimos 5 años formación (con la correspondiente acreditación) en Buenas Prácticas Clínicas, con el objetivo de analizar si aquellos que cuentan con dicha formación tienen un mayor conocimiento de los textos de bioética seleccionados. Por último, para conocer el grado de conocimiento de los cuatro documentos de bioética seleccionados (Declaración de Nüremberg, Informe Belmont, DoH y Guía CIOMS), los participantes debían responder si habían leído cada uno de los documentos (íntegra o parcialmente), si lo conocían aunque no lo hubieran leído, o bien si les era completamente desconocido. Para los objetivos de este estudio, se consideró un buen conocimiento el haber leído íntegra o parcialmente el documento.

El cuestionario se distribuyó entre una muestra de conveniencia integrada por los miembros del CEI y algunos servicios del hospital con amplia trayectoria en investigación. La participación fue voluntaria y anónima. Los criterios de selección de los participantes fueron: cualquier tipo de profesional (médicos, enfermera/os, farmacéuticos, biólogos u otras titulaciones) con experiencia en investigación clínica en los últimos 10 años (como investigador principal o bien como colaborador) y/o con experiencia como miembro de un CEI.

Se realizó un análisis descriptivo de los resultados utilizando SPSS versión 15.0 y se compararon los resultados de conocimiento de cada uno de los documentos con diferentes características de los participantes mediante una prueba de Chi-cuadrado o test de Fisher según el caso.

TABLA 1. Resultados sobre el conocimiento de los cuatro documentos de todos los participantes.

	Lectura íntegra n (%)	Lectura parcial n (%)	Conoce pero no ha leído n (%)	Desconoce el documento n (%)
Declaración de Helsinki	16 (22%)	36 (48%)	16 (22%)	6 (8%)
Informe de Belmont	11 (15%)	9 (12%)	10 (13,5%)	44 (59,5%)
Código de Nüremberg	9 (12%)	17 (23%)	19 (26%)	29 (39%)
Guía CIOMS	4 (5%)	12 (16%)	23 (31%)	35 (47%)

RESULTADOS

Setenta y seis individuos aceptaron participar y contestaron el cuestionario. Dos de los cuestionarios fueron rechazados por no cumplir los criterios de selección (los sujetos no tenían experiencia como investigadores y/o pertenencia a un CEI).

De los 74 cuestionarios evaluables, 51 (69%) correspondían a mujeres. La mediana de edad, en el 89% de los casos, se situó entre los 30-59 años. La mayoría de participantes eran médicos (46, 65%), enfermeros (11,15%), biólogos (10, 14%), farmacéuticos (3, 4%) y el resto tenía otras titulaciones. Cuarenta y cinco de los encuestados (61%) tenían experiencia como investigadores principales de estudios promovidos por la industria farmacéutica o independientes, y 51 (69%) habían realizado formación reciente acreditada en BPC. Once de los participantes (15%) eran o habían sido miembros de un CEI. De estos, 7 (64%) tenían además experiencia como investigadores principales.

De todos los participantes, 52 (70%) afirmó que conocía al menos parcialmente el texto de la DoH, 26 (35%) el código de Nüremberg, 20 (27%) el informe Belmont y 16 (22%) la guía del CIOMS. Dieciséis individuos (un 22% de la muestra) habían leído íntegramente la DoH (Tabla 1).

De los 45 encuestados que tenían experiencia como investigadores principales en estudios clínicos (promovidos por la industria farmacéutica o en proyectos independientes), 32 (71%) declararon un buen conocimiento de la DoH (10 la habían leído completamente), así como el 100% de los que pertenecían o habían pertenecido a un CEI. De estos, 6 individuos (54,5%) habían leído el texto completo de la DoH. En lo que respecta a los 51 sujetos que tenían formación en BPC, un 74% declararon un buen conocimiento de la DoH y 12 (51%) la habían leído íntegramente. Sobre la posible asociación entre tener un buen conocimiento de la DoH y haber sido investigador principal, tener formación en BPC o haber pertenecido a un CEI, solo en este último caso se observó una asociación estadísticamente significativa, aunque debe tenerse en cuenta el escaso número de participantes de este grupo en la interpretación de este resultado (Tablas 2 a 4).

TABLA 2. Resultados sobre el conocimiento de la DoH en función de la experiencia como IP.

	Lectura íntegra o parcial de la DoH n (%)	No lectura de la DoH n (%)	Valor de p
IP n=45	32 (71%)	13 (29%)	1,000
No IP n=29	20 (69%)	9 (41%)	

TABLA 3. Resultados sobre el conocimiento de la DoH en función de la formación en BPC.

	Lectura íntegra o parcial de la DoH n (%)	No lectura de la DoH n (%)	Valor de p
Formación en BPC n=51	38 (74,5%)	13 (25,5%)	0,277
No formación en BPC n=23	14 (61%)	9 (39%)	

TABLA 4. Resultados sobre el conocimiento de la DoH en función de la pertenencia al CEI.

	Lectura íntegra o parcial de la Declaración de Helsinki n (%)	No lectura de la Declaración de Helsinki n (%)	Valor de p*
Miembro de CEI n=11	11 (100%)	0 (0%)	0,027
No miembro de CEI n=63	41 (65%)	22 (35%)	

**Prueba exacta de Fisher.*

DISCUSIÓN/CONCLUSIONES

Los resultados obtenidos indican que el conocimiento de la DoH de los encuestados es razonablemente adecuado ya que un 70% ha leído de forma íntegra o parcial el documento. Estos resultados son superiores a otras encuestas publicadas, que muestran un conocimiento de la DoH que va de un 6,67% entre 30 profesionales de la salud en Santiago de Cuba[8], un 10% entre trabajadores de un Hospital en Barbados[9], un 11,8-14,4% en un hospital terciario de Nepal[10], un 16% en profesionales sanitarios de un hospital psiquiátrico de Shangai[11], casi un 22% entre médicos profesores y residentes de un hospital en India[12],

un 34,8% de miembros de diferentes Facultades de Odontología del norte de la India[13], o un 40% entre las enfermeras del Hospital Universitario de Tokushima en Japón[14], pero son menores que los publicados en dos hospitales universitarios de Kyoto en Japón o de Seúl en Corea del Sur, en los que el 74% y 97% de los médicos entrevistado dijeron conocer la DoH, respectivamente[15]. La encuesta de estos dos hospitales incluyó preguntas sobre algunos aspectos de la DoH que requerían haberla leído o conocerla bien, en este caso el porcentaje de conocimiento real bajó al 57% y 63%, respectivamente.

Los resultados de conocimiento general respecto a los otros documentos son superiores en nuestra muestra a los publicados para el código de Nüremberg o Informe Belmont, que está en la mayoría de casos entre el 11-15%. Destacar que el documento menos conocido es la Guía de la CIOMS con porcentajes del 3-10%[12,13].

En cuanto a las características de los investigadores en relación a su conocimiento de los documentos éticos, cabe destacar que el hecho de ser investigador principal, investigador colaborador, tener experiencia en investigación independiente o promovida por industria sanitaria o tener un curso de Buenas Prácticas Clínicas no influye en las respuestas, dato que resulta sorprendente, ya que al menos en los ensayos clínicos es obligatorio hacer constar que se procederá de acuerdo con la DoH. Por el contrario, el hecho de realizar actividad evaluadora en un CEI sí que se relaciona con un mejor conocimiento.

Nuestros resultados tienen limitaciones debidas en parte al diseño y al instrumento utilizado. Se trata de un estudio preliminar y por ello el número de participantes es limitado. La muestra puede no ser representativa del total de unos 350-500 investigadores del centro. La distribución entre profesionales de enfermería ha sido muy limitada. Para poder realizar un análisis estadístico mínimo se han agrupado en las comparaciones a aquellos que habían leído de forma íntegra o parcial los documentos. De nuevo el tamaño muestral podría influenciar los resultados al no alcanzar una potencia estadística suficiente. No se han recogido datos sobre el tipo de estudios, que podría ser variable, aunque cualquier investigador debería conocer como mínimo la DoH. Por otro lado, podría haber una sobreestimación de los que dicen conocer los documentos, especialmente entre los investigadores principales y miembros de CEI, aunque el carácter anónimo de la encuesta podría haber ayudado a su veracidad.

Como conclusiones, parece claro que en nuestro medio, hospital universitario de tercer nivel, el conocimiento íntegro de la DoH solo llega a una cuarta parte de los profesionales, si bien casi un 70% la ha leído de forma íntegra o parcial. Los resultados para otros documentos son más bajos, lo que resulta lógico al ser,tanto el el Código de Nüremberg como el Informe Belmont, la fuente de la DoH. En el caso de CIOMS, su extensión y profundidad explicarían que fuera más conocida entre personas más interesadas en bioética de la investigación. Por nuestros resultados, parece de interés hacer un esfuerzo para que los investigadores clínicos mejoren sus conocimientos sobre los documentos de referencia sobre experimentación en seres humanos, especialmente aconsejar la lectura íntegra de la Declaración de Helsinki.

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SWOT analysis at research Valencian Ethics Committees

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BACKGROUND

Ethics Committees (REC) are undergoing a paradigm shift from the promulgation of Law 14/2007. Currently, the main challenges include reviewing the evaluation methodology to adapt to the new deadlines for evaluation and response required and take advantage of new information technologies to facilitate the process of documentation, evaluation and issuance of the opinion; And at the same time, with a quality management system to guarantee the safety and welfare of people involved in a research project. On the other hand, the excessive bureaucracy to which these committees are submitted, and the increasingly short deadlines for responding to them are requires.

OBJECTIVE

Through an analysis of strengths, weaknesses, opportunities, and threats (SWOT), we explored the strengths and weaknesses of the internal environment and the opportunities and threats of the external environment of in an attempt to provide recommendations aimed at maximizing REC services in Valencia.

METHODS

We use a qualitative approach, through a semi-structured questionnaire, with open and close questions related to strengths (REC values), opportunities (circumstances that may favor RECs), weaknesses (factors to avoid, which should be improved, future disadvantagesor) and threats (obstacles, threats that may completely impede the activity). All RECs (n = 22) were invited to participate, through an email. The invitation is accompanied by a short explanation, and is sent on March, 2017, via an email from the technical secretariat of the Program of clinical studies of medicines and health products (PECME). A period of two weeks is given to answer it, and a reminder is sent 48 hours before the end of the term.

RESULTS

A 27% of the REC completed the questionnaire. In order of relevance: strengths (group experience, PECME support, participatory process and altruistic), opportunities (incentive for the quality of research, possibility of support from other institutions), weaknesses (lack of time, resources, motivation and recognition; following by lack of training, information and communication) and threats (bureaucracy, perception of lack of support, widespread disenchantment, normative changes).

The SWOT analysis revealed several strengths and opportunities, which can better equip RECs in the quest to maximize the quality of research. Moreover, the analysis also highlighted areas of weaknesses as well as current threats which include bureaucracy, perception of lack of support also in normative changes. Two major recommendations emerge from this research. The first is the need of a continue training in methodology and ethic in research and recognition of RECs members. The second recommendation is the need of government support, especially when normative changes succeeded.

Theme 1: continuum training in methodology and ethic in research

Participants highlighted the lack of incentives, continue training, internal and external support, lack of recognition as one of the largest weaknesses of today's RECs. This situation calls for better coordination establishing "Standard Work Procedures" and looking to the future Decree in which the requirements will be established minimum to be able to evaluate clinical trials with medicinal. Here the role of Clinical Pharmacologist is essential. Clinical Pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans involving health care, teaching, and research with expertise also in Research Methodology and Ethics.

Also, important changes in the clinical information systems are expected to have an impact on the organization of care. The progressive generalization of electronic records within settings and the platform of social security have allowed for shared information. Input of electronic data should help to RCE work but the effort to keep the confidentiality must be higher.

Theme 2: the need of government support and recognition of RECs members work

Support is a key issue for people who are at RECs (i.e. time, institutional recognition of their activity and recognition) even more when normative changes succeeded. Therefore, it was considered necessary that the institutions provide the technical means and resources necessary to its technical secretariats.

LIMITATIONS OF THE ANALYSIS

REC,s member consultation can help identify strengths and weaknesses for health care reforms in a specific context. We tried to ensure that all important groups be consulted but we arise only response from near a quarter of RECs. The researchers had diverse backgrounds, being mostly 50% Clinical Pharmacologist.

CONCLUSIONS

SWOT can provide a potential strategic point to guaranty the quality of research. In our REC, members experience and support are essential being bureaucracy and lack of time factors to improve. These findings provided useful insights surrounding perceived priorities.

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Strenthening ethics review in Uzbekistan

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ABSTRACT

After Uzbekistan had declared its independency country was faced a transformation of the economy as well as the social system. Principles of economics influenced healthcare system as a result medicine became commercialized. A lot of foreign pharmaceutical companies offered collaboration to conduct clinical trials. As a consequence, there was raised question on protection of research participants' rights. The government paid more attention and played a key role in safeguarding rights of its citizens.

In different countries, Research Ethics Committees (REC) are organized in different ways. There is no established structure of ethics committees. It is difficult to say how many RECs needed to guarantee effectiveness of review process because the number of RECs not correlated with the quality of review.

In Uzbekistan there are seven ethics committees: National Ethics Committee (NEC) with its 5 regional branches, and Bioethics Committee (BC) of the Association of Physicians of Uzbekistan. In their activity NEC operates according to national policy and international standards. Composition of the NEC/REC directly affects the quality of the ethical analysis process and the level of the research participants' protection. To ensure the interests of all stakeholders NEC/REC should include enough number of members. NEC in Uzbekistan has 35 members from different fields. It includes professionals with clinical practice experience such as physicians together with specialists in activities related to medical research such as scientists and pharmacologists.

Usually NEC members are competent in medicine, pharmaceutical practice, except ethics. NEC reviews only clinical studies applied by pharmaceutical companies. Scientific researches are out of ethics review process.

One of the assurance of quality of ethics review is education of REC members. Based on above description first step for ensuring quality of review, protecting the research participants in biomedical research and to meet international ethics standards there is an urgent necessity to strengthening NRC/RECs and BC activity through training their members.

Evaluation about the studies evaluated by the CEIm before and after the implementation of RD 1090/2015

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OBJECTIVE

The new European regulation [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][1] sets out, on the one hand, common procedures for clinical trial authorization throughout Europe, but on the other hand, leaves outside of this cooperation those aspects of an intrinsically national nature, requiring assessment by each Member State.

The RD1090/2015 (Royal Degree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry)[2] implementation sets Spain in one of the first countries that has modified its legislation with the aim of adapting as soon as possible to the new European regulation and thus maintaining a competitive position in the European and global context of clinical research.

This RD introduction was accompanied by the need to create a "Collaboration memo" specifying the responsibilities of the Ethics Committee for investigation with medicinal products (CEIm) and of the Spanish Agency of Medicines and Medical Devices (AEMPs)[3]. From the beginning, our center was involved in the design and improvement of this "Collaboration memo". It might be said that our CEIm restructuration based on the new RD was completely established on April 2016.

The primary objective of this project is to analyze the number and type of the studies evaluated by our CEIm during two periods of time: before and after the introduction of the new RD in order to know if it had been changes in the CEIm activity because of this implementation.

METHODOLOGY

An observational retrospective study of clinical trials and post-authorization observational studies (EPAs) CEIm evaluations during two periods: From April 1, 2015 to March 31, 2016 (period I) and from April 1, 2016 to March 31, 2017 (period II). The information was

extracted from our database system, where all the studies in which our hospital participates are included.

RESULTS

During the period I (p.I), 236 clinical trials were register in our database, 214 (90.7%) were drug trials and 22 with MD (9.3%). Between these trials, our Reference Committee (old RD nomenclature) evaluated 37 (a 15.7%).

During the period II (p.II), 226 clinical trials were register in our database, 196 (86.7%) were drug trials and 30 with MD (13.3%). As a CEIm, a total of 49 trials (21.7% of the registrations) were evaluated.

In relation to EPA evaluations, during p.I there was evaluated 153 studies against the 177 of the p.II. Inside this studies, there were 45 (p.I) against 49 (p.II) of EPA-OD (Other designs), 37 (p.I) against 46 (p.II) EPA-noEPA (study without characteristics of EPA), 29 (p.I) against 42 (p.II) EPA with MD, 35 (p.I) against 30(p.II) EPA-SP (Prospective control), 4 (p.I) against 5 (p.II) EPA-LA(EPA that requires requirement of the regulatory authorities), 2 (p.I) against 3 (p.II) EPA-AS (Security EPA) and 1(p.I) against 2 (p.II) classified like others.

CONCLUSION

Comparing both periods, it can be observed that the total number of clinical trials evaluated are similar. However, there has been a 25% increase of the CEIm evaluations. This percentage supposes a big enhance of the activity not only for this increase but for the complexity of the evaluations.

This situation could be explained with the fact that all the Reference Committees that worked before the new RD implementation could not join the "Collaboration memo". Moreover, between the members of this group[4], only those that meet predefined conditions will be accredited as a CEIm[5].

The EPAs evaluation has increased too but in a 13.6%. EPA with MD has shown the most relevant increase (31%). Although this EPA classification was already consolidated in the old RD[6], we will see in the near future several changes in Europe that will make administrative processes easier and will probably simplify these evaluations.

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Preparing the implementation of the EU Regulation 536/2014 in Romania. Recommendations: the creation of a national database of biomedical studies and a centralized system of the Ethics Committees (ECs)

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One of the key points of the new Regulation, the EU database, is supposed to bring "a sufficient level of transparency"[1] in clinical trials. The following aspects are addressed: the public accessibility, the easily searchable format and relevant data and documents. The impact would also enhance the research ethics system from Romania. Nevertheless, its implementation has to consider the country's current situation and the necessities of the national ethics review system. Related to the Regulation, it was nationally adopted in May 2016[2]. An English version plus a translated one are available on the sites of the main institutions responsible for biomedical ethics review[3,4].

The creation of a national centralization for ECs (National and Institutional Ethics Committees-IECs), alongside their work, is recommended. Information related to the efficacy of ECs' work may be found on some of their sites, for example, on the national ethics committees' sites, such as on the page of the National Committee of Medicines and Medical Devices (NCMMD), who is one of the main institutions responsible for the ethical review of a clinical trial or for an investigational medicinal product[3]. Also, relevant information may be found on the page of the National Agency for Medicines and Medical Devices (NAMMD), who is the other main institution who provides procedure steps for assessment and approval of applications for clinical trials with human medicine[4]. Related to IECs, ME-COPP Ro, a longitudinal research focused on the institutionalization of ethics in Romanian organizations *(7 types of organizations public institutions, health care institutions, universities, mass media institutions, non-governmental organizations, political parties and companies),* underlined the following information: IECs do not have an informative role regarding the awareness of ethics issues, most of the times they are regarded as "domestic institutions" and information about them can be offered only by the affiliated institutions. Also, the legislation offers to IECs a sort of "close" status[5] and according to the Law No. 206/2004, Art. 9(1), related to the good conduct of scientific research, development, technology and innovation, they are considered as "institutions that are part of the national system of research and development and/or the institutions who conduct programs of research and development, alongside the institutions which are responsible for the dissemination of the results (and) are also responsible for the compliance with the norms and ethical values of research and development" (Art. 9(2))[6]. However, if information about IECs are

required or searched by the general public, the following are relevant: *9 universities do not have a person responsible for public relations regarding the activity of RECs, 14 universities do not have a phone number for the persons responsible for such information, and 13 universities do not have an email address concerning the above, 19 universities do not make available information about the work of IECs, the membership, and contact data*[7]. In addition, for the moment, there is no procedural interaction between the national committees (NCMMD, NAMMD) and the IECs during the approval process of either bio-medical research applications (including clinical research other than clinical drug trials, research with biological materials) or non bio-medical research applications. The research proposals can be submitted in parallel to the national competent authority and to the IECs. Therefore, there is no official and national centralization of their work, or of the efficacy of their work, and information related to their activity are hardly available. As a general picture, an oversight of the national committees and IECs may not be done for the moment with a centralized mechanism. The report related to their work must be searched separately, on each of the ECs' sites (where these are available).

Regarding the information offered to the general public, a more structured pattern may be seen on the national ethics committees' pages. However, there are not linked together the study's summary, the protocol and the clinical study report or notifications of the start of a clinical trial and of the end of the subjects' recruitment, as indicated for the future EU database. Therefore, the centralization could fill the gaps mentioned above, alongside information about the number of the ECs, their role, their activity, the interaction between them, the contact information. Thus, the centralization has to be related to a national database for biomedical studies; at the moment there is no such centralization. This will significantly influence the review and oversight process of biomedical studies and it will ease the networking from different types of ECs. Moreover, it could create a procedural interaction between the national committees and the IECs during the approval process of bio-medical research applications and it will increase the level of transparency.

However, even if these recommendations are the ideal case, for a feasible and successful implementation, some additional aspects need to be considered, like the politics and the economic freedom. Related to the economic freedom, according to The Heritage Foundation/ The Wall Street Journal (2012), the general index of economic freedom is 64.4, score that places Romania on the 62 position from 179, a fact that points out a moderate economic freedom[8]. Thus, the financial resources allocated to ECs are limited and the centralization could create a possible burden for the national budget scheme. Moreover, the excessive polarized political system and the apparent reluctance of Romanian politics at being transparent are not to be neglected. An example of the apparent reluctance of transparency may also be seen in the situation related to IECs, described above. Closely related to the economic freedom, the political freedom is another factor that influences the development of the ECs from my county. Furthermore, the distrust in politics is also shaped by the corruption who complete the global picture, as the European Commission reported in 2012, "in Romania, there is an excessive polarized political system, where the distrust in political entities and the accusation are a common model"[8].

Related to what may be done to overcome the barriers to a proper functioning of the ECs from my country and the development of a mechanism of oversight the ECs and their work,

the following possibilities may be useful, some of them being adapted from "Communication strategy of the National Agency for Medicines and Medical Devices"[9]:

- Adequate procedures to facilitate communication between ECs.
- A better strategy for the national budget alongside more funds for the appropriate financing of ECs.
- More staff trained for communication.
- Regional, national or international meetings for ECs' members, as World Health Organization recommends ("oversight mechanisms include regional or national meetings for the purpose of exchanging information about best practices, or partnerships between committees from different countries"[10]).
- More transparency, as the Regulation (EU) no. 536/2014 recommends for the EU database and which could be adapted also to a possible national database ("in order to ensure a sufficient level of transparency in the clinical trials, the EU database should contain all relevant information as regards the clinical trial submitted through the EU portal. The EU database should be publicly accessible and data should be presented in an easily searchable format, with related data and documents linked together by the EU trial number and with hyperlinks" (67)[1]). The transparency must be also applicable for the subjects of the studies: "The subject shall be informed that the summary of the results of the clinical trial and a summary presented in terms understandable to a layperson will be made available (...) irrespective of the outcome of the clinical trial, and, to the extent possible, when the summaries become available (6)[1]". ECs must continue to develop the highest degree possible of transparency in decision-making and make the information available to the general public under their regulatory scope.
- *A centralized system of all the ECs and their work, under a national database of biomedical studies.*

The national situation and possible recommendations like those specified have to be linked to increase the level of efficacy and transparency of ECs to benefit the implementation of the new EU regulation, at least regarding the EU database which will favor the exchange of information about best practice from different countries. It could also represent a further step regarding the European conceptual framework of ethical research.

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El procedimiento del consentimiento informado en los ensayos clínicos: conocimiento y percepciones de los médicos de familia

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INTRODUCCIÓN

Los ensayos clínicos controlados y aleatorizados con medicamentos (ECm) son el principal método científico para obtener el máximo grado de evidencia sobre la eficacia de nuevos tratamientos[1,2].

Para respetar la autonomía y bienestar del participante, es obligatorio la obtención del consentimiento informado (CI), tal y como lo indica la Declaración de Helsinki[3] y otros documentos[4-6].

Las Guías de Buena Práctica Clínica recomiendan informar al médico de Atención Primaria (MAP) sobre la participación de sus pacientes de cupo en ECm[7]; sin embargo, en el CI no siempre está claramente especificado[8,9]. Si bien en algunos CI se anima a los participantes a consultar/informar a sus respectivos MAP, o se señala que será el propio investigador quien lo comunicará, la inclusión del MAP en el proceso del CI no está regulada.

En España, una fracción importante de participantes en ECm son pacientes oncológicos[10], con comorbilidades de base y que acuden al Centro de Salud con frecuencia. Para una buena praxis clínica, a la hora de prescribir medicamentos, en el momento de interpretar nuevos síntomas o signos que puedan tener relación con el fármaco de estudio administrado, así como por temas de seguridad, sería importante que el médico conociera la participación de su paciente en un ensayo y las características del mismo.

En un estudio realizado por nuestro grupo en el año 2016[11], un 69% de los CI revisados contemplaban la posibilidad de informar al MAP (en 46 de 67 ensayos clínicos), si bien no se analizó el cumplimiento y efectividad de dicha comunicación.

El objetivo de este trabajo es analizar el grado de conocimiento de los MAP sobre la participación de sus pacientes de cupo en ECm.

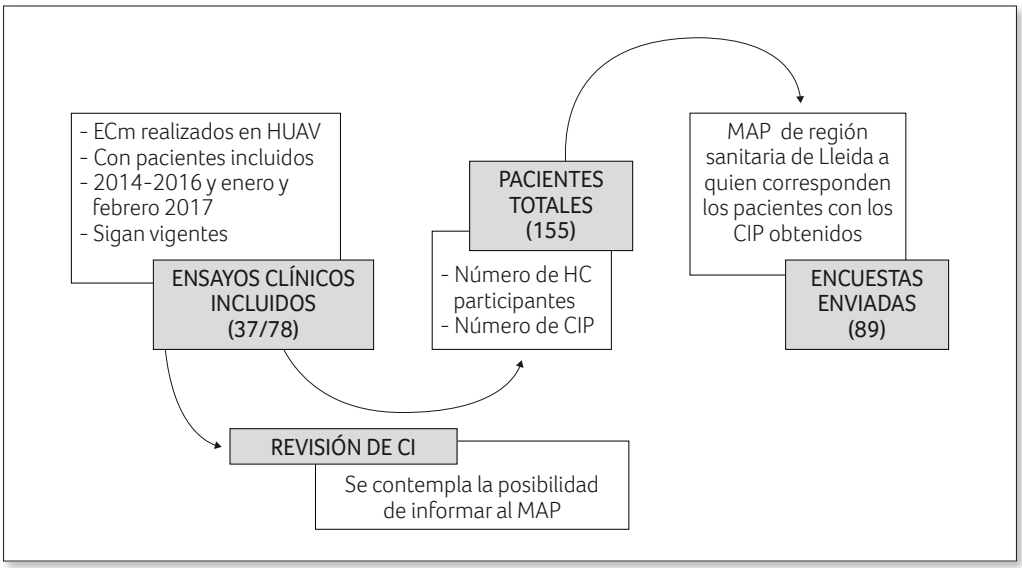

FIGURA 1. Esquema del estudio.

MATERIAL Y MÉTODOS

Se realizó un estudio transversal observacional a propuesta del propio Comité de Ética de la Investigación, y se seleccionaron aquellos ECm vigentes realizados entre enero de 2014 y febrero de 2017 con pacientes incluidos. Se identificaron un total de 37 ensayos.

A continuación, a partir de los registros de participación y los CIP de los pacientes (n=155) se identificó a los respectivos MAP (n=89 médicos, ya que algún médico tenía más de un paciente de su cupo participando en algún ECm). Se diseñó un cuestionario anónimo y una carta de presentación para los MAP seleccionados que se envió por correo interno desde la Dirección de Atención Primaria de Lleida. Se dejó un plazo de un mes para recibir respuestas (17/03/2017-17/04/2017). Los datos han sido tratados de forma anónima y confidencial (Fig. 1).

RESULTADOS

De los 89 cuestionarios enviados, se obtuvieron 41 respuestas (46,0%).

Los resultados obtenidos se presentan a continuación. Cabe decir que algunas de las preguntas de elección múltiple del cuestionario enviado permitían más de una respuesta.

Un 82,0% de los médicos conocía que tenían algún paciente de su cupo participando en un ECm y de estos, un 75,0% creía recordar el número de pacientes (recordaban un total de 93 participantes) (Fig. 2).

Un 28,0% de los MAP fue informado a través de una carta proporcionada por el paciente y un 34% a través de la Historia Clínica Informatizada (HCI) sin ninguna alarma. En ningún

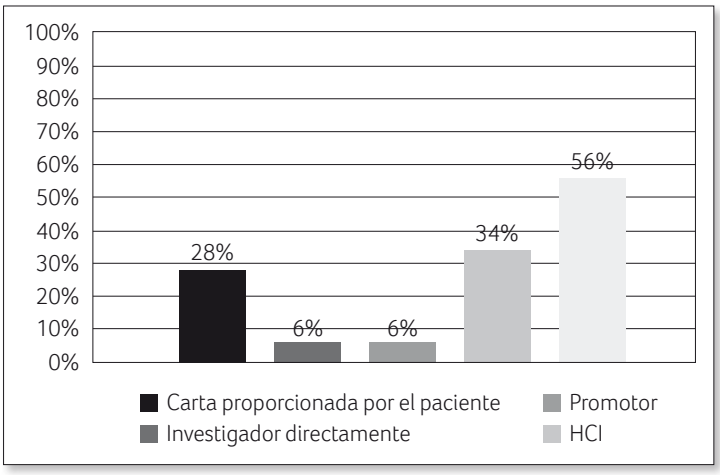

FIGURA 2. Método por el que el médico de familia fue informado de la participación de sus pacientes en ensayos clínicos con medicamentos.

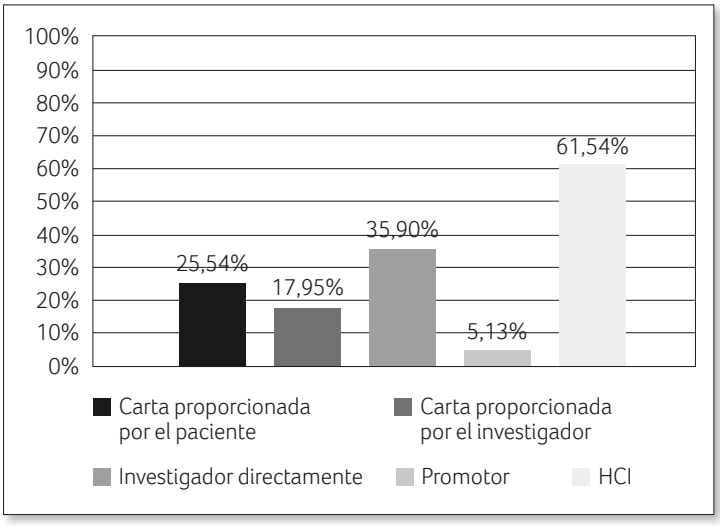

FIGURA 3. Preferencias de los médicos de familia del procedimiento para ser informados de la participación de sus pacientes en ensayos clínicos con medicamentos.

caso el MAP recibió una carta del investigador; y únicamente un 6,0% fue comunicado a través del investigador y otro 6,0% mediante el promotor. Un 56,3% de los MAP respondió la opción de otros sistemas de comunicación, refiriendo que el paciente le proporcionó la información verbalmente en la consulta.

Prácticamente todos los médicos (97,4%) consideraron que era importante que se informara sobre la participación de sus pacientes en ECm y que no debería ser opcional (74,0%); aunque un 18,0% consideraba que era el paciente quien debería decidir y un 5,0% el investigador (Fig. 3).

Por otro lado, la mayoría de MAP preferiría recibir dicha comunicación mediante una alarma/señal en la HCI (61,5%) o una carta entregada por el investigador (35,9%). En menor proporción, a través de una carta proporcionada por el paciente (25,5%) o a través del investigador (17,9%) y únicamente un 5,1% a través del promotor. Nadie optó por otra opción no propuesta.

Finalmente, se dejó la opción de dar una opinión, y un 20,0% aprovechó esta posibilidad. Un 5,1% manifestó que se sentía desinformado, mientras que un 12,8% remarcaba la importancia del tema y un 2,6% opinó que debería aceptarse informar al MAP en el momento de firmar el CI.

DISCUSIÓN

Este estudio nos aproxima al grado de conocimiento del MAP sobre la participación de sus pacientes en ECm. Nuestro estudio muestra que la mayoría de médicos recibe dicha información verbalmente a través del paciente. Este procedimiento puede dar información incompleta o distorsionada; pero seguramente es la vía empleada debido a la confianza y la relación interpersonal que existe entre paciente y médico[12]. De hecho, en nuestro estudio realizado en el 2016, el 70% de los pacientes referían haber comunicado verbalmente a su MAP su participación en un ECm[11].

La comunicación con los MAP pensamos que es un aspecto a clarificar en el CI, por la seguridad del paciente, para evitar interferir con algún otro fármaco en los resultados del ensayo clínico y para garantizar una atención médica adecuada. El MAP es la puerta de entrada al sistema sanitario y quien mejor conoce al paciente. Cada paciente tiene características bio-psico-sociales diferentes que podrían influir en los resultados del ECm y en la salud del participante[12], si bien es cierto que los ECm se realizan principalmente en el ámbito hospitalario[13]. La HCI permite el intercambio de información entre ambos niveles asistenciales[14,15] y, según nuestros resultados, es la vía preferida de los MAP para conocer la participación de sus pacientes en ECm (señalando además que sería deseable que apareciera una alarma o marca visible en la HCI que avisara de la participación).

En nuestro estudio previo[11], prácticamente todos los pacientes pensaban que era importante que se informara a su MAP, siendo un aviso en la HCI el método preferido, coincidiendo con la opinión de los MAP. Adicionalmente, los MAP refieren la importancia de tener conocimiento sobre los medicamentos administrados a sus pacientes en el curso del ECm; para ello, se podría adjuntar en la HCI la hoja informativa del EC o un enlace al respectivo ECm en el Registro Español de Ensayos Clínicos (como base de datos pública que sirve como fuente de información de ECm y se puede acceder gratuitamente desde la página web de la AEMPS)[16] o en ClinicalTrials.gov (como página del NIH que proporciona a pacientes, familiares, profesionales de la salud, investigadores y público, un fácil acceso a la información sobre estudios clínicos en una amplia gama de enfermedades y condiciones)[17].

Cabe decir que en algún tipo de ECm, por el tipo de medicamento administrado, duración del estudio y ámbito sanitario en el que se realiza (patología, características de los pacientes...) puede tener todavía una mayor relevancia la información al MAP. En el presente estudio, todos los ensayos clínicos eran con fármacos y principalmente, con medicación oncológica. Esto pudo influir a la hora de comunicar al MAP la participación en el ECm por parte del paciente. Sin embargo, pensamos que se debería informar a los MAP de la participación de sus pacientes en ECm de manera sistemática. Además, la vía de comunicación para informar al MAP (carta, HCI, personalmente) se debería especificar en el CI y se debería hacer un seguimiento de si se cumple con el proceso.

Nuestros resultados son similares a los de Giménez[18]. En este estudio realizado en Terrassa, se describe que en un 50,0% de CI se aconsejaba a los pacientes consultar con sus respectivos MAP, un 96,0% de MAP consideraba importante recibir dicha información y que únicamente un 33,0% la recibía[18]. Un 60,0% de médicos recordaba tener pacientes participantes en ensayos clínicos y en el 76,0% de los casos, fue el paciente quien lo comunicó al médico[18]. Un 85,0% de los MAP mostró insatisfacción con la información recibida[18].

Finalmente estamos de acuerdo en señalar que los MAP son los especialistas más cercanos al paciente y que su colaboración puede facilitar el proceso de reclutamiento y soporte, así como la finalización y seguimiento de los pacientes en los ECm[19]. Asimismo, podrían cumplir el papel de educador[20] o asesor[21] para facilitar la comprensión del CI, ya que diversos estudios han demostrado una compresión subóptima del CI[22,23].

En definitiva, pensamos que se debería contemplar, respetando la autonomía y confidencialidad del paciente, un sistema reglado y fiable de comunicación a los respectivos MAP pues beneficiaría a todos los implicados en los ECm.

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The outlook of institutional research ethics in Lithuanian University of Health Sciences

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The increasing importance of institutional ethical review of student level research is widely recognized. Obviously, the governmental national or regional research ethics committees (REC) play the most significant role in research ethics review system, however it should be recognized that some realms of research involving human subjects are not covered by REC. According to the new edition of CIOMS guideline 23: "All proposals to conduct health-related research involving humans must be submitted to a research ethics committee to determine whether they qualify for ethical review and to assess their ethical acceptability, unless they qualify for an exemption from ethical review"[1]. The increasing scale of such proposals as well as the enormous load of review process has naturally led to the idea of sharing the functions and activities between REC and IRB or UREC.

Apart from the strict regulations of RECs' activities to revise, evaluate and approve (or not) the scientifically sound and socially valuable research projects (likewise, clinical trials or population genetic studies) initiated by qualified scientists or pharmaceutical companies or other certified institutions, the review of "lower" (student) level of research was traditionally left to a sort of "small brother" of REC, traditionally named as an Institutional Review Board (IRB). In particular, mostly all biomedical research projects at the undergraduate student level were conventionally delegated to a variety of all possible types of IRB, for instance, university (or medical school) based research ethics committees (UREC) developed in the European context.

For instance, in Lithuania, "the division of responsibilities and accountability between national and local bodies is clearly defined in different normative documents" and only national Lithuanian Bioethics Committee and regional RECs "issue decisions on clinical drug trials and on biomedical research studies"[2]. However, university based REC or other type of ethical review unit at the institutional level was left to be regulated autonomously by institution statutes or other initial regulations in accordance to national laws.

The purpose of this contribution is to discuss some issues of ethical review process of student level human-related research. Beside typical challenges at the institutional research ethics bodies the paper reflects students' feedback to research ethics institutionalization at the Bioethics Center based at one of major medical schools in the Baltic States, namely, Lithuanian University of Health Sciences (LUHS).

The Bioethics Center (BEC) at LUHS was established and has been operating as a university research ethics committee (UREC) for more than 10 years. The BEC is being regulated and is accountable to the Senate of LUHS. The emergence of the BEC was stipulated by the institutional changes which inter alias promoted student engagement into research activities, and thus, student research was integrated into the curriculum. At the time the Bioethics Center at LUHS (with representatives from all faculties in the BEC board) is officially responsible for the revision and approval of student research and other educational projects related to human research. Beside the mentioned general functions of ethical review, the mission of the BEC is also aimed to educate the undergraduate students as well as academic community (for instance, supervisors) by developing the awareness of such concepts as academic integrity, academic freedom, transparency, confidentiality or preventing any forms of scientific misconduct in research practice. In other words, the BEC at LUHS was assumed to be responsible for the application of the research ethics principles, international guidelines or national legal requirements of human-related research in undergraduate student research level. Accordingly, the development of practical skills of research ethics (such as preparation of necessary documents, including the elaboration of informed consent form etc.) are recognized and adopted at the institutional level, which means that any biomedical research involving human subjects conducted within the university by undergraduate students should be reviewed and approved. It should be noted that nearly all student research projects (at least in Lithuanian University of Health Sciences) are initiated by student scientific societies or proceeded as final thesis for bachelor or master graduation (depending on the program) and required to be supervised by teaching professors, scholars or medical doctors. Any type of research on animals or other type studies not related to human subject (i.e. in life sciences) are excluded from the scope of the BEC jurisprudence. The scale of research project reviews has increased up to 800 per year.

However, some challenges have unsurprisingly occurred while achieving such ambiguous goals. Just to illustrate the some featuring issues in ethical review of student led research, the results of recent pilot survey are to be employed. The pilot survey cross-sectional survey was conducted on March and April, 2017. The study sample included forty randomly selected students who admitted the Bioethics Center at LUHS for approval of their research projects. The majority of them (N=37, response rate - 92.5%) volunteered to participate and respond to the originally developed anonymous questionnaire. It consisted of 12 close and open style questions aimed to reveal students approach to various aspects of research ethics institutionalization at university level.

Overall, for the most part of the respondents were medical students (70 %), the rest were nursing (16 %), public health (11 %) and dentistry (3 %) students; majority of respondents (76 %) were female, and all of them reported they have had some classes on research ethics.

The analysis of findings of this survey have revealed the tendency of shortage of "organized skepticism" (in Mertonian terms), or, in other words, some disrepancies of students' critical reflection regarding their engagement into scientific research. In particular, all students reported they were institutionally required to start develop their research competencies through empirical studies as well as to prove their abilities to conduct scientific research. However, most of the respondents (78 %) did not consider their own research as meaningful and important to their future career. Additionally, they reflected their research projects as

having little risk or no risk at all to research participants, but at the same time it was assumed of having very little scientific value (mostly, retrospective secondary analysis of databases or analysis of patients' files). Accordingly, third of them did not plan to publish their research data even in the student conference or further and considered it just as another formality to overcome. In such a context, some scholars claim that "as learning objectives associated with student research can be met without the need of human subjects', and so "the benefit associated with training new health care professionals cannot, itself, justify such a risks" to participants of the study"[3].

Secondly, the application of major principles and legal regulations of ethical review of student research activities was regarded as too ambitious and too demanding or even leading to annoying bureaucracy. For example, to get the BEC approval to conduct a survey in the same university hospital, students should make the contract with the Service of Coordination of Research and Studies and obtain the signatures on the agreement from the heads of all units included into their research. Nearly two thirds of respondents of the survey reported that they were asked to improve their application forms due to mistakes or missing details in the informed consent forms or other required documents. Accordingly, the same respondents reported a deficient of practice of the informed consent procedures during their research preparation. On other hand, students' involvement in some research projects was recognized as interesting but at the same challenging, for example, in the preparation of informed consent forms according to new legal requirements.

The survey also revealed that few hours of research ethics training incorporated into course of Medical Ethics or Bioethics are not sufficient. Accordingly it might be presumed that faculty administrators, architects of curricula, the educators as well as BEC members in LUHS and other institutions should seek for new models of efficient and collaborative student participation in research. One of many examples could be the development of nursing curricula which aims "to help students develop a research skill set that articulates with rapid career advancement of gifted, young graduates interested in research"[4].

Eventually, a number of questions how to cope with institutional requirements and student demands at the level of student research review system arise. One of them is how to balance the responsibility sharing among the stakeholders involved into research, i.e. students, researchers, their supervisors, institutions (i.e. University Hospital) and the university based research ethics committee likewise the BEC at LUHS. According to the survey, one of four respondents assumed that only research supervisor (but not student) should bear the moral responsibility and consequences of student research projects, which indicated some potential mismatches between being "student" and "researcher" at the same. On other hand, no respondents indicated the potential conflicts of interest in their studies and assumed this issue as mostly not valid at the student level research. Some concerns regarding legitimacy of the applicability of the BEC approval for publication reasons were also expressed.

In conclusion, the development and perspectives of Bioethics Center at LUHS should be harmonized with national RECs and should gain the best practices from similar European university research ethics committees. Despite the apparently less important role of such university based research ethics institutions comparing to REC, both share the mission to protect the rights of research participants and advocate their interests in biomedical research.

To find the best way to accomplish the undertaken duties in the ethical review of student research, the further discussion and more comprehensive studies are needed. Finally, the functions and procedures of university research ethics centers or similar institutional bodies that advocate research ethics values might rather be compared and accordingly improved at the international level.

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Retos para el informe de evaluación en ensayos clínicos con menores[1]

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MOTIVACIÓN

La investigación biomédica se debe realizar en libertad con los límites establecidos en la ley que garanticen la protección del ser humano. Así lo viene a reconocer como regla general el art. 15 del Convenio de Oviedo de 1997. Pues bien, resulta esencial garantizar que los ensayos clínicos se realizan con todas las garantías establecidas para la protección de la persona, y en particular en el caso de los menores.

MARCO NORMATIVO DE LOS ENSAYOS CLÍNICOS

A nivel internacional vamos a destacar[1] la Declaración Universal sobre Bioética y Derechos Humanos de 19 de octubre de 2005 (DUBDH) en el marco de la UNESCO (Organización de las Naciones Unidas para la Educación, la Ciencia y la Cultura), que si bien no hace referencia a los ensayos clínicos en particular, sí especifica como objetivo de la misma el reconocimiento de la importancia de la libertad de investigación científica, pero en el marco de de los principios éticos que la Declaración destaca y respetando la dignidad humana, los derechos humanos y las libertades fundamentales (art. 2 d DUBDH); así como la Convención de Derechos del Niño de 1989[2].

A nivel del Consejo de Europa debemos considerar dos instrumentos de gran importancia y vinculantes para España, como son el Convenio Europeo de Derechos Humanos (CEDH) y el Convenio de Oviedo, antes citado. A nivel de la Unión Europea debemos considerar la Carta de Derechos Fundamentales de la Unión Europea (CDFUE), mereciendo especial atención el

[1]También sería importante hacer referencia a la Declaración de Helsinki sobre los principios éticos para las investigaciones médicas en seres humanos, aprobada por la Asamblea General de la Asociación Médica Mundial; así como en relación a la eventual participación de niños en ensayos clínicos.

[2]Cuyo objeto es la protección de los derechos del niño a la vez que procura garantizar su autonomía. Por ello es relevante tener en cuenta que el art. 5 del mismo establece que los Estados parte respetarán las responsabilidades, derechos y deberes de los padres o tutores, a la vez que el art. 11 obliga a garantizar al niño "que esté en condiciones de formarse un juicio propio, el derecho a expresar su opinión libremente en todos los asuntos que afectan al niño, teniéndose debidamente en cuenta las opiniones del niño, en función de la edad y madurez del niño".

art. 3, puesto que a la vez que se reconoce el derecho de toda persona a su integridad física y psíquica (art. 3.1), se establece que "en el marco de la medicina y la biología se respetarán en particular" (art. 3.2):

"a) el consentimiento libre e informado de la persona de que se trate, de acuerdo con las modalidades establecidas por la ley;

b) la prohibición de las prácticas eugenésicas, en particular las que tienen como finalidad la selección de las personas;

c) la prohibición de que el cuerpo humano o partes del mismo en cuanto tales se conviertan en objeto de lucro;

d) la prohibición de la clonación reproductora de seres humanos".

Dicho lo cual, conviene hacer referencia al ya no tan reciente Reglamento (UE) nº 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014, sobre ensayos clínicos de medicamentos de uso humano (en adelante, Reglamento 536/2014)[3], que introduce una serie de cambios importantes (1, p. 1)[4] en búsqueda de la simplificación de la regulación de los ensayos clínicos pero con el objetivo de mantener las garantías esenciales para los participantes[5]. Sin embargo, aún no ha entrado en vigor[6]; continuando vigente la Directiva 2001/20/CE del Parlamento Europeo y del Consejo, de 4 de abril de 2001, relativa a la aproximación de las disposiciones legales, reglamentarias y administrativas de los Estados miembros sobre la aplicación de buenas prácticas clínicas en la realización de ensayos clínicos de medicamentos de uso humano[7].

España se ha adelantado a la entrada en vigor del Reglamento 536/2014 aprobando el Real Decreto 1090/2015, de 4 de noviembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos (RD1090/2015), y que adapta la legislación española a la nueva normativa europea, y que entró en vigor el 13 de enero de 2016[8].

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[3]Reglamento (UE) nº 536/2014 del Parlamento Europeo y del Consejo, de 16 de abril de 2014, sobre ensayos clínicos de medicamentos de uso humano, DOUE 27.5.2014. Como veremos, para adaptarse a esta nueva normativa europea el legislador español ha aprobado el Real Decreto 1090/2015, de 4 de noviembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.

[4]Como dice GARCIA VIDAL, entre las novedades podría citarse por ejemplo la introducción de una nueva definición de "ensayo clínico", que se integraría junto al "estudio observacional" dentro de un concepto más amplio de "estudio clínico" (1, p. 1).

[5]Téngase en cuenta que el considerando 83 del Reglamento deja claro que el mismo respeta los derechos fundamentales y observa los principios reconocidos en la Carta, concretamente "sobre dignidad humana, integridad de la persona, los derechos del menor, el respeto de la vida privada y familiar, la protección de datos de carácter personal y la libertad de las artes y de las ciencias".

[6]En efecto el R536/2014 dispone que su entrada en vigor será a partir de seis meses después de la publicación del aviso que se contempla en el art. 82.3 del mismo, "pero en ningún caso antes del 28 de mayo de 2016", y estamos a la espera del comienzo de su vigencia, que como sabemos será de aplicación directa en todos los Estados miembros.

[7]Directiva 2001/20/CE del Parlamento Europeo y del Consejo, de 4 de abril de 2001, relativa a la aproximación de las disposiciones legales, reglamentarias y administrativas de los Estados miembros sobre la aplicación de buenas prácticas clínicas en la realización de ensayos clínicos de medicamentos de uso humano (DOCE, 1.05.2001 L. 121/34-44).

[8]Aunque el instrumento elegido por la Unión Europea ha sido el de Reglamento para garantizar la utilización de procedimientos comunes para la autorización de ensayos clínicos en la UE, ha dejado en manos de los Estados miembros algunas cuestiones y aspectos relevantes que deben definirse y concretarse a nivel nacional, de tal forma que es esencial la existencia de una norma nacional.

Hay que resaltar que aunque la Ley 14/2007, de 3 de julio, de Investigación biomédica (LIB)[9], incluye la investigación de carácter básico y la clínica con la excepción de los ensayos clínicos con medicamentos y productos sanitarios remitiéndose a su normativa específica (art. 1.3), el art. 43 de la misma hace referencia a los ensayos clínicos al tratar la utilización de líneas celulares o de muestras biológicas; y que el Real Decreto 1716/2011 de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica (RD 1716/2011)[10] que desarrolla parte de la LIB, puesto que a pesar de que excluye de su ámbito de aplicación a los ensayos clínicos con medicamentos y productos sanitarios, incluye la regulación de "las muestras biológicas de origen humano que hayan sido obtenidas en ensayos clínicos con medicamentos y productos sanitarios, una vez terminado el ensayo clínico correspondiente y siempre que entren a formar parte de una colección o de un biobanco" (art. 3.1 d RD 1716/2011). Esto ha motivado ciertas dudas de interpretación sobre la aplicabilidad de la LIB y el RD 1716/2011 únicamente a las muestras biológicas derivadas de ensayos clínicos cuando entren a formar parte de una colección o de un biobanco, o también en otros supuestos (3, p. 108).

LOS ENSAYOS CLÍNICOS

Concepto de ensayos clínicos

Definido el marco normativo debemos entrar en la problemática del concepto de "ensayos clínicos", precisando que nos referimos a ensayos clínicos con medicamentos. El RD1090/2015, reproduciendo el Reglamento 536/2014 define el "ensayo clínico" como "estudio clínico" -concepto más amplio que incluye por ejemplo los estudios observacionales o la práctica clínica habitual- que cumple cualquiera de las condiciones previstas (art. 2.1 h RD1090/2015)[11]. Además, se introduce en la nueva normativa (art. 2.1 j) RD1090/2015, y art. 2.2 3) Reglamento 536/2014) un tipo específico de ensayo clínico, el "ensayo clínico de bajo nivel de intervención" que debe cumplir una serie de estrictas condiciones[12].

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[9]Ley 14/2007, de 3 de julio, de Investigación biomédica (BOE núm. 159, de 4.07.2007)

[10]Real Decreto 1716/2011 de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica (BOE núm. 290, de 2.10.2011).

[11]"1.º Se asigna de antemano al sujeto de ensayo a una estrategia terapéutica determinada, que no forma parte de la práctica clínica habitual del Estado miembro implicado. 2.º La decisión de prescribir los medicamentos en investigación se toma junto con la de incluir al sujeto en el estudio clínico. 3.º Se aplican procedimientos de diagnóstico o seguimiento a los sujetos de ensayo que van más allá de la práctica clínica habitual."

[12]"1.º Los medicamentos en investigación, excluidos los placebos, están autorizados. 2.º Según el protocolo del ensayo clínico: 1.ª Los medicamentos en investigación se utilizan de conformidad con los términos de la autorización de comercialización; o 2.ª el uso de los medicamentos en investigación se basa en pruebas y está respaldado por datos científicos publicados sobre la seguridad y eficacia de dichos medicamentos en investigación en alguno de los Estados miembros implicados. 3.º Los procedimientos complementarios de diagnóstico o seguimiento entrañan un riesgo o carga adicional para la seguridad de los sujetos que es mínimo comparado con el de la práctica clínica habitual en alguno de los Estados miembros implicados."

Condiciones y requisitos de realización de los ensayos clínicos

La nueva normativa sobre ensayos clínicos constituye sin duda un avance significativo en una regulación más armonizada de los ensayos clínicos con medicamentos, permitiendo una simplificación de la tramitación administrativa de los mismos. No obstante, establece una serie de requisitos para su realización. Así, están sujetos a una autorización previa de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) tras una evaluación científica y ética (art. 17.1 y 2b) RD 1090/2015), y es preciso el dictamen favorable emitido por un Comité de Ética de la Investigación con Medicamentos (CEIm) que será único y vinculante (art. 17.2b) RD 1090/2015); y la conformidad de la dirección del centro participante que se manifestará en la firma del contrato entre el promotor y el centro o bien mediante conformidad expresa en el caso de que el promotor/investigador pertenezca al centro (art. 17.2c) RD 1090/2015). Hay que tener en cuenta que la evaluación por parte del CEIm y la AEMPS se basará en lo previsto en los arts. 6 y 7 del Reglamento 536/2014 (art. 20 RD1090/2015) incluyendo **los beneficios terapéuticos y para la salud pública que se esperan,** los riesgos e inconvenientes para el sujeto del ensayo, el cumplimiento de los requisitos de fabricación e importación de medicamentos en investigación y auxiliares, cumplimiento de requisitos de etiquetado, si el manual del investigador es completo y adecuado (I parte, art. 7 Reglamento 536/2014); el cumplimiento de los requisitos de consentimiento informado, el resarcimiento o compensación cumplen los requisitos, así como la compensación para los investigadores, el cumplimiento de la normativa europea de protección de datos (el Reglamento habla de la Directa 95/46/CE, pero hay que entender que se refiere a la norma que esté vigente), así como la idoneidad de las personas que realizan el ensayo clínico (art. 49 Reglamento 536/2014)[13] la idoneidad de los centros de ensayo clínicos (art. 50 Reglamento 536/2014)[14], existencia de seguro, garantía u otro mecanismo de indemnización de los daños y perjuicios que pueda sufrir el sujeto del ensayo (art. 76 Reglamento 536/2014), y las normas de recogida, almacenamiento y uso futuro de las muestras biológicas del sujeto de ensayo (art. 8 Reglamento 536/2014).

En este sentido, el art. 3.1 del RD 1090/2015 dispone que únicamente se podrá iniciar un ensayo clínico cuando el CEIm y la AEMPS hayan considerado que se cumplen la totalidad de las condiciones previstas en el mismo. Se establece la obligación de realizar los ensayos clínicos de acuerdo con la Declaración de Helsinki y de tiendo en cuenta el Convenio de Oviedo "así como a cualesquiera otras normas que pudieran resultar de aplicación" (art. 3.2 RD 1090/2015); y como ya hemos visto, en caso de que el ensayo prevea la recogida de muestras biológicas, se ajustará al RD 1716/2011.

Además es esencial el consentimiento informado (art. 4 RD 1090/2015). Se establecen ciertas particularidades para la realización de ensayos clínicos con menores (art. 5 RD 1090/2015), con personas con la capacidad modificada para dar su consentimiento (art. 6

[13]El investigador debe ser un médico conforme al Derecho nacional o un profesional que el Estado miembro implicado considere cualificado para ser investigador por reunir los conocimientos científicos y de experiencia necesarias, y las demás personas que participen deben estar adecuadamente cualificadas por educación, formación y experiencia (art. 49 Reglamento 536/2014).

[14]Las instalaciones deben ser adecuadas para la realización del ensayo clínico conforme a los requisitos del Reglamento (art. 50 Reglamento 536/2014).

RD 1090/2015)[15], ensayos clínicos con mujeres embarazadas o en período de lactancia (art. 8 RD 1090/2015), y los ensayos clínicos en situaciones de urgencia (art.7 RD 1090/2015).

Los ensayos clínicos con menores[16]

Además de cumplir las condiciones previstas para cualquier ensayo clínico es necesario cumplir las condiciones establecidas en el art. 32 del Reglamento 536/2014 (art. 5.1 del RD 1090/2015)[17]. Esto es congruente con lo previsto en el art. 10 del Reglamento 536/2014, que establece unas consideraciones específicas sobre colectivos vulnerables, entre los que incluye los menores, en cuyo caso "se prestará una atención específica a la evaluación de la solicitud de autorización de un ensayo clínico a partir de la experiencia en pediatría o recabando asesoramiento sobre los problemas clínicos, éticos y psicosociales específicos de la pediatría".

Por último, será necesario haber obtenido el consentimiento informado previo de los padres no privados de la patria potestad[18] o del representante legal del menor, a quien deberá oírse si siendo menor de doce años tuviera suficiente juicio. Además, será necesario el consentimiento del menor "cuando las condiciones del sujeto lo permitan y, en todo caso, cuando el menor tenga doce o más años, deberá prestar además su consentimiento para participar en el ensayo (art. 5.3 RD 1090/2015).

Doble consentimiento

La norma española utiliza el margen que le da el Reglamento europeo en el art. 29.8 al referirse a los menores para disponer la posibilidad de que el Derecho nacional pueda exigir además del consentimiento informado del representante legal -que se exige en todo caso para los menores en el art. 32.1 a), el consentimiento del propio menor cuando este tenga capacidad de formarse una opinión y de evaluar la información que se le facilite; introduciendo así un doble consentimiento (3, p. 258).

La norma española parece haber sido amplia en este sentido al exigir el consentimiento del menor una vez tiene doce o más años "en todo caso", y también "cuando las condiciones

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[15]Es importante señalar que, de conformidad con lo previsto en el art. 2.3 del Reglamento, un sujeto de ensayo que responda a la vez a las definiciones de menor y de sujeto incapaz, se considerará como sujeto incapaz. Se entiende como "sujeto incapaz" aquel sujeto de ensayo que "por razones distintas a las de la edad legal para dar su consentimiento informado, no es capaz de prestar su consentimiento informado, según la normativa del Estado miembro implicado (art. 2.1 19) Reglamento).

[16]El Reglamento 536/2014 deja en manos de los Estados miembros, debido a que la normativa nacional difiere mucho, la determinación de las normas sobre los representantes legales de personas incapaces y menores, que requieren de medidas de protección específica (Considerando 27 del Reglamento 536/2014).
El art. 2 del Reglamento es el que incluye las definiciones a efectos de aplicación del mismo, y entiende por "menor" al "sujeto de ensayo que, según la normativa del Estado miembro implicado, no ha alcanzado la edad legal para dar su consentimiento informado" (art. 2.18 536/2014).

[17]Esta remisión al art. 32 del Reglamento, sin su reproducción en la norma, y posteriormente una regulación específica de los ensayos con menores va a plantear problemas de interpretación, que en todo caso deben llevar a aplicar con prevalencia el art. 32 del Reglamento. Además, el CEIm encargado de evaluar la parte II de un ensayo clínico con menores "debe contar entre sus miembros con expertos en pediatría o haber recabado asesoramiento sobre las cuestiones clínicas, éticas y psicosociales en el ámbito de la pediatría" (art. 5.2 del RD 1090/2015).

[18]El documento de consentimiento informado de los padres será válido siempre que vaya firmado por uno de ellos con el consentimiento expreso o tácito del otro que debe quedar suficientemente documentado, conforme al art. 156 del Código Civil.

del sujeto lo permitan"; de tal forma que debemos entender que la retirada de cualquiera de los dos consentimientos, indistintamente, sería suficiente para que el sujeto se retirara del ensayo clínico.

En cualquier caso, las dudas que se pueden suscitar en caso de conflicto por la existencia de un consentimiento (bien de los padres /representante legal o del menor capacitado para emitirlo) y la ausencia del otro, deben llevar a entender que no cabe realizar el ensayo clínico; y esto porque si por un lado entendemos que el consentimiento del menor capacitado para emitir el consentimiento es esencial porque su oposición impide el ensayo o se puede retirar en cualquier momento (ex art. 32.1 c) Reglamento, que luego comentaremos), el consentimiento de los padres o del representante legal también va a ser esencial tanto por exigencia del propio Reglamento (ex art. 32.1 a)), como a la luz de la jurisprudencia del TEDH en M.A.K. y R.K c. Reino Unido (2010)[19]. Y lo cierto es que esto puede afectar a la autonomía del menor que quiere someterse a un ensayo clínico, mientras que sus representantes legales no, y cabría preguntarse si en estos casos habría que someterlo a decisión judicial en interés del menor.

Oposición del menor con capacidad de formarse una opinión y evaluar información

Se echa de menos en la norma nacional la inclusión de la eventual oposición del menor con capacidad de formarse una opinión y evaluar información.

Cabe preguntarse si cuando la el art. 5.3 hace referencia al consentimiento del menor "cuando las condiciones del sujeto lo permitan" se refieren a este supuesto, o más bien está exigiendo que tenga una madurez suficiente para poder consentir, que implicaría algo más. Lo cierto es que el art. 32.1 c) Reglamento otorga eficacia a la negativa del menor con capacidad de formarse una opinión y evaluar información, y ello aunque la ley nacional no prevea la necesidad o exigencia de su consentimiento, de tal forma que podríamos decir que en todo caso aunque puede que el consentimiento de este menor capaz de formarse una opinión pueda no ser necesario por no requerirlo la ley nacional, su negativa sí va a operar y a tener eficacia en virtud de la norma europea una vez entre en vigor por su efecto directo (3, p. 258-259); es más también tendrá eficacia su voluntad de retirarse del ensayo, pues se establece que *"el investigador respeta el deseo explícito de un menor, capaz de formarse una opinión y evaluar la información a que se refiere el artículo 29, apartado 2, de negarse a participar en el ensayo clínico o de retirarse en cualquier momento"* (art. 32.1 c) del Reglamento 536/2014).

Además, hay que tener en cuenta que habiendo dado el consentimiento el representante legal, cuando el menor alcance la edad para consentir deberá recabarse su consentimiento para poder continuar con el ensayo clínico (art. 4.3 RD 1090/2015). Hay que decir que la norma española aquí peca de laxitud porque no dice claramente como debe ser el consentimiento, mientras que el Reglamento es claro al exigir que el consentimiento sea expreso[20].

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[19]STEDH 23 de marzo de 2010, M.A.K. y R.K c. Reino Unido Nos. 45901/05 y 40146/06, en la que se condena al RU por la toma de sangre para la realización de un test y una fotografía sin el consentimiento de los padres. Aunque es un caso de sospechas médicas de abuso sexual por parte del padre, viene a establecer la necesidad del consentimiento de los padres y/o representante legal.

[20]Así, el art. 32.3 establece que si el menor alcanza la edad legal para prestar su consentimiento durante la realización del ensayo clínico "se obtendrá su consentimiento informado expreso antes de que pueda continuar con su participación en el ensayo clínico".

CONCLUSIONES

Hemos analizado el marco normativo aplicable a los ensayos clínicos con menores, y en particular las nuevas disposiciones del Reglamento europeo, y la norma española que lo incorpora, para tratar de identificar los retos que pueden encontrar los Comités a la hora de elaborar el informe de evaluación.

Del marco normativo analizado se deduce la necesidad de proteger de forma especial al menor en la realización de ensayos clínicos, sometiendo estos a unos requisitos especiales que se deben dar, y dando una especial importancia a la autonomía del menor, cuando esto es posible.

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Research Ethics Committees: an experience in higher education

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ABSTRACT

This communication aims to present the need for the creation of a Research Ethics Committee at an institution of higher education, specifically in a school of health.

Technical and scientific developments requires an ethical reflection. Law Nº 21/2014 of 16 April, which regulates clinical research, creates a new frame of reference for clinical research with human beings in Portugal. Recognizing, however, the respective specificities, the same law generalizes to all areas of clinical research ethics review scheme, as well as the discharge of responsibilities of the sponsor, the investigator, the monitor and the clinical study. Sets the clinical studies with intervention, felt the need to assess the ethical point of view, the research carried out at school. Also, EU Regulation 536/2014 on the Research Ethics Committees of different European countries, sets in art. 2-2-c) "clinical trial with minimal intervention" which includes "... diagnostic procedures or additional monitoring."

Some of the studies conducted in the courses taught, fall within this scope, which apply in private clinics without ethics committees, in the community and/or at the pedagogical clinic in institution, relevant to creating a Research Ethics Committee, although there is no national regulation specifies for this typology of the Ethics Committee.

In order to address this need, it is an Ethics Committee at school that took office on 18 March 2015, whose members come from different areas of knowledge – nursing, bioethics, Clinical Physiology, physiotherapy, medicine, law and sociology.

The Commission shall be guided by a regulation itself, has drawn up a set of documents and rules for the submission of projects.

Organised three public seminars to disclosure on issues in the field of ethics, and in partnership with the pedagogical council organized a training session in the current school year, about "the Ethics Committee of the ESALD and the same Circuits", directed to all students that are in the development phase of study projects, and framed in the investigation curricular unit each of first and second cycle courses.

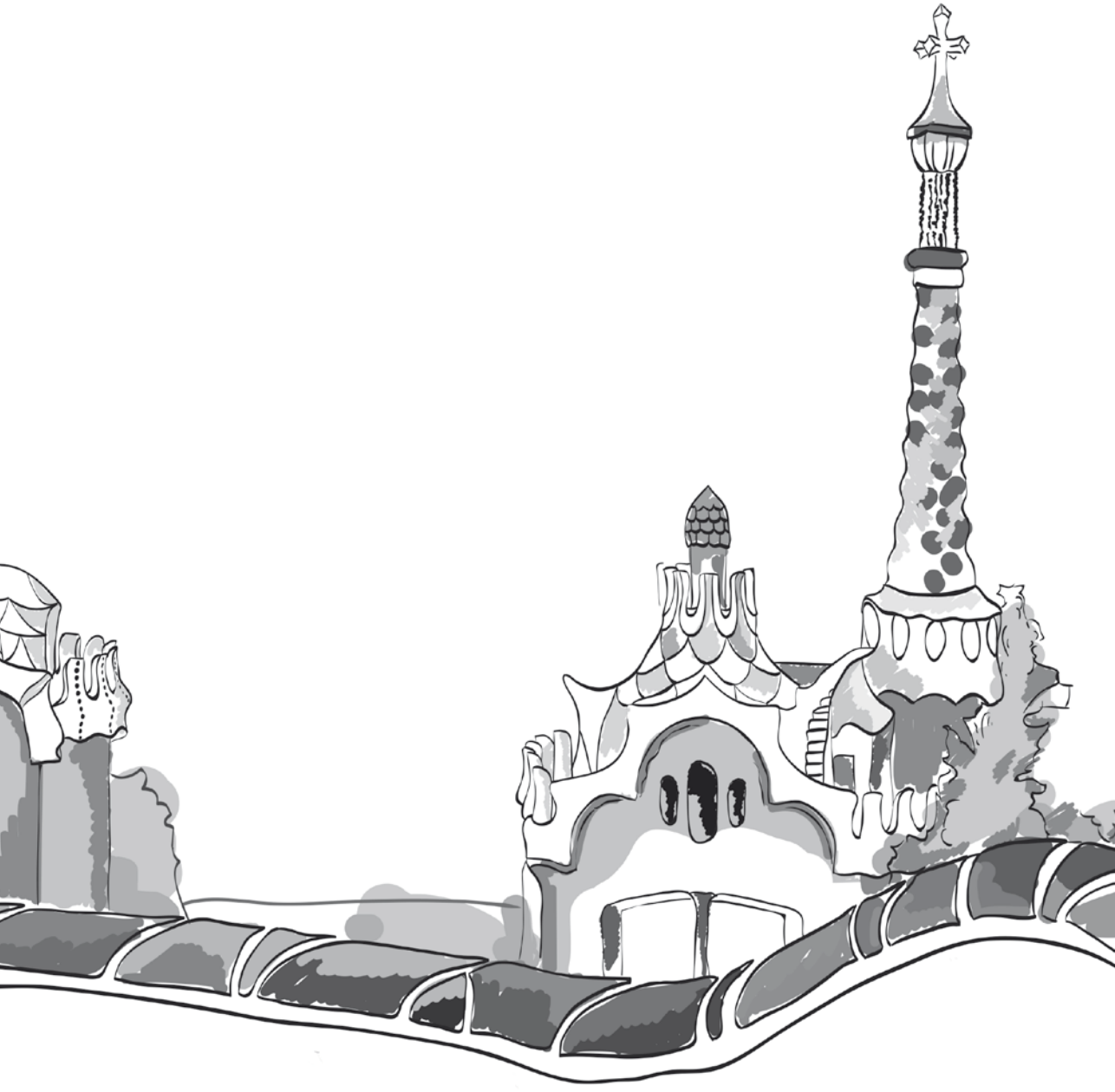
To date present, the Commission has analysed, recorded and issued an opinion on 43 projects.

The main objective, as referred Casado et al, is to "Create a culture of integrity in the scientific community and in the institutions of higher education that encompasses all areas

of knowledge and research." In the Declaration on research integrity in responsible research and innovation (2016:74).

The importance of research ethics committees, is to defend the human rights of the vulnerable person when a study participant, and diminish the scientific fraud and make the fundamental research for the development of science and knowledge.

Our experience is recent, but has been important to ensure good practice, the precision and the ethical principles in scientific research.



POSTERS

Bioethics Committees: classification, structure and operation

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INTRODUCCIÓN

Un Comité es, según el diccionario, "un conjunto de personas encargadas por ley, o por una corporación o autoridad, de ejercer unas determinadas competencias permanentes o entender en algún asunto específico". De acuerdo a esta definición podemos entender, por Comité de ética en al ámbito de la Biomedicina, como el grupo de personas que se constituyen con la misión de deliberar sobre la moralidad de determinadas decisiones o cursos de acción, bien sea en la práctica clínica, en la investigación científica o en la gestión de los recursos sanitarios disponibles.

Warren Reich en su *Enciclopedia de Bioética* involucra un nuevo término que es importante para la conformación de los comités: la interdisciplinariedad. Para Reich la Bioética se encarga del estudio sistemático de las dimensiones morales –incluyendo la visión moral, las decisiones, las conductas y las políticas– de las ciencias de la vida y del cuidado de la salud, usando una variedad de metodologías éticas en un contexto interdisciplinario.

En conclusión podemos afirmar que los Comités de Bioética son instancia o estructuras interdisciplinarias de diálogo y decisión bioética, es decir, que asumen la responsabilidad de intentar clarificar y resolver racional y razonadamente los conflictos de valores que se presentan en la investigación, en la práctica clínica y actualmente, en las organizaciones sanitarias.

Los Comités de Bioética se pueden clasificar según la tabla 1.

Examinaremos a continuación las particularidades de cada uno de los Comités, insistiendo en los Comités de Ética Hospitalaria y los Comités de Ética de la Investigación mejor implementados y normalizados en nuestros países latinoamericanos.

COMITÉS DE ÉTICA HOSPITALARIA

Momentos clave en la constitución de los Comités de ética hospitalario o asistencial:

- 1960. El Dr. Belding Screibner se inventa procedimientos para realizar diálisis renal. Se crea en Seattle el primer Centro de diálisis y se ve obligado a hacer una selección de pacientes que pueden beneficiarse de esta nueva técnica. Se crea un Comité *ad hoc* para determinar entre los pacientes cuya indicación es correcta, cuáles son los criterios

TABLA 1. Clasificación de los Comités de Bioética.

Nombre	Finalidad	Denominación
1. Comités de ética de la Investigación	Velar por la calidad de la investigación en seres humanos y la protección de los mismos	USA: *Institutional Review Boards* (IRB´s). Colombia: Comités de Ética de la Investigación Biomédica
2. Comités de ética asistencial u hospitalaria	Resolver los conflictos éticos que plantea la asistencia hospitalaria y elaborar protocolos asistenciales para los casos en que se necesite establecer políticas institucionales	USA: *Hospital Ethics Comites.* Colombia: Comités de Ética Hospitalario
3. Comité de ética de las organizaciones sanitarias	Deliberar sobre los valores relevantes para una organización de salud, que son las que la definen internamente y la diferencian externamente, así como de su aplicación a todos los procesos (clínicos y de gestión) que realiza dicha organización en orden a convertir la organización en una institución de excelencia	España: Comité de Ética de las Organizaciones Sanitarias
4. Comisiones Nacionales de Bioética	Asesorar permanente o temporal, generalmente a los diversos gobiernos nacionales en diferentes temas de Bioética	USA: *The President´s Commission for the Study of Ethical problems in Medicine and Biomedical and Behavioral Research.* Colombia: Comité Intersectorial de Bioética

de selección, que no obedecen a indicaciones médicas. El Comité duro muy poco, ya que el gobierno federal patrocinó los gastos del tratamiento de todos los enfermos con necesidad de diálisis.

- 1968. La Facultad de Medicina de la Universidad de Harvard publica en la Revista *JAMA* la conclusiones de un Comité *ad hoc* sobre la definición de muerte cerebral. Este informe será el origen de la conformación do comités en hospitales para decidir cuándo se dan las condiciones de muerte del tronco encefálico y las posibilidades éticas y legales de desconexión de la respiración asistida de los pacientes.
- 1970. El Dr. Ned H. Cassem preside el primer Comité de ética asistencial en el Hospital General de Massachussets para determinar el manejo de pacientes terminales.
- 1971. El neorólogo Cranford crea en el *Hennepin Country Medical Center* el comité denominado *Thanatology Committee,* para decidir sobre problemas médicos, éticos y legales en el tratamiento con pacientes terminales.
- 1973. Se comienzan a publicar artículos en revistas especializadas sobre la importancia de crear comités de ética asistencia en los hospitales norteamericanos. La doctora Karen Teel es la primera en escribir una serie de artículos que va ser tomados en cuenta por el Tribunal Supremo de New Jersey a la hora de dar sus conclusiones en el caso de Karen Ann Quinlan.

- 1976. El Tribunal Supremo de New Jersey determina que el Comité de ética asistencial del hospital en el que esta Karen Ann Quinlad en estado de coma profundo, debe declarar si el pronóstico de irreversibilidad de vida cognitiva es correcto. De ser así, el Tribunal podrá autorizar la petición de los padres adoptivos de Karen de desconectarla de la respiración asistida. Con gran sorpresa se desconectó a Karen suponiendo una muerte por apnea, pero Karen siguió respirando espontáneamente, muriendo diez años más tarde en su casa debido a una neumonía.
- 1978. Se crean Comités de ética asistencia supranacionales debido al nacimiento de la primera niña "probeta", Louise Joy Brown, como resultado de una fecundación *in vitro* y transferencia embrionaria realizada en Inglaterra.
- 1983. La Comisión creada por el Presidente Jimmy Carter [*The President´s Commission for the Study of Ethical Problems in Mediciona and Biomedical and Behavioral Research* (1980)] recomienda en uno de sus informes *(Deciding to Forego Life-sustaining Treatment)* la creación de Comités de ética asistencia para tomar decisiones éticamente correctas en los casos de pacientes incapaces mentalmente, pacientes inconscientes y en recién nacidos gravemente enfermos.
- 1984. El Departamento de Salud y Servicios Humanos de Estados Unidos y la Academia Americana de Pediatría recomiendan la creación de Comités de Bioética en hospitales, para los estudios de los problemas éticos en neonatología, así como para la capacitación del personal y la elaboración de normas institucionales.

Funciones

Véase la figura 1.

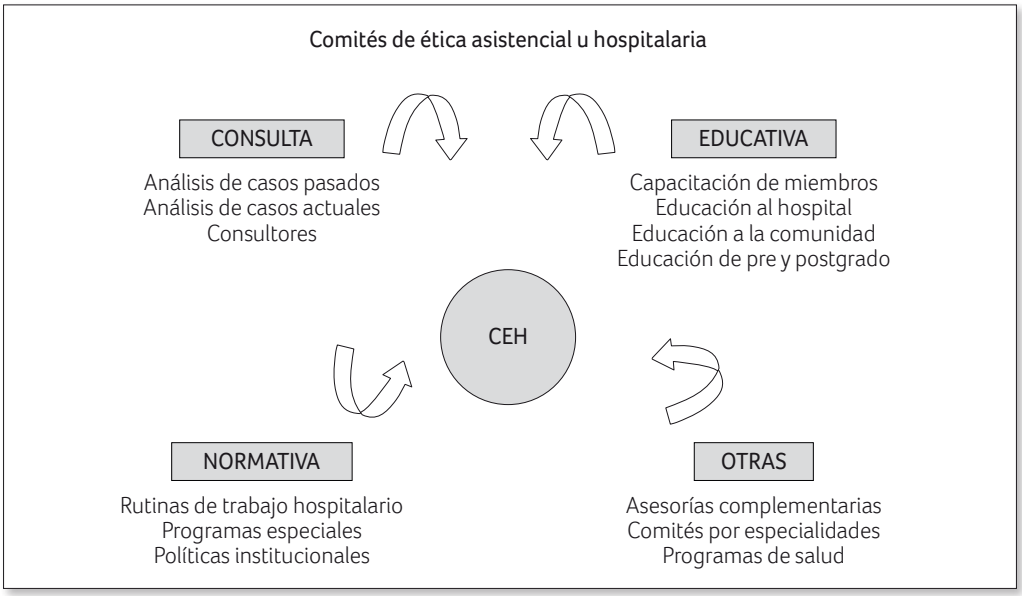

FIGURA 1.

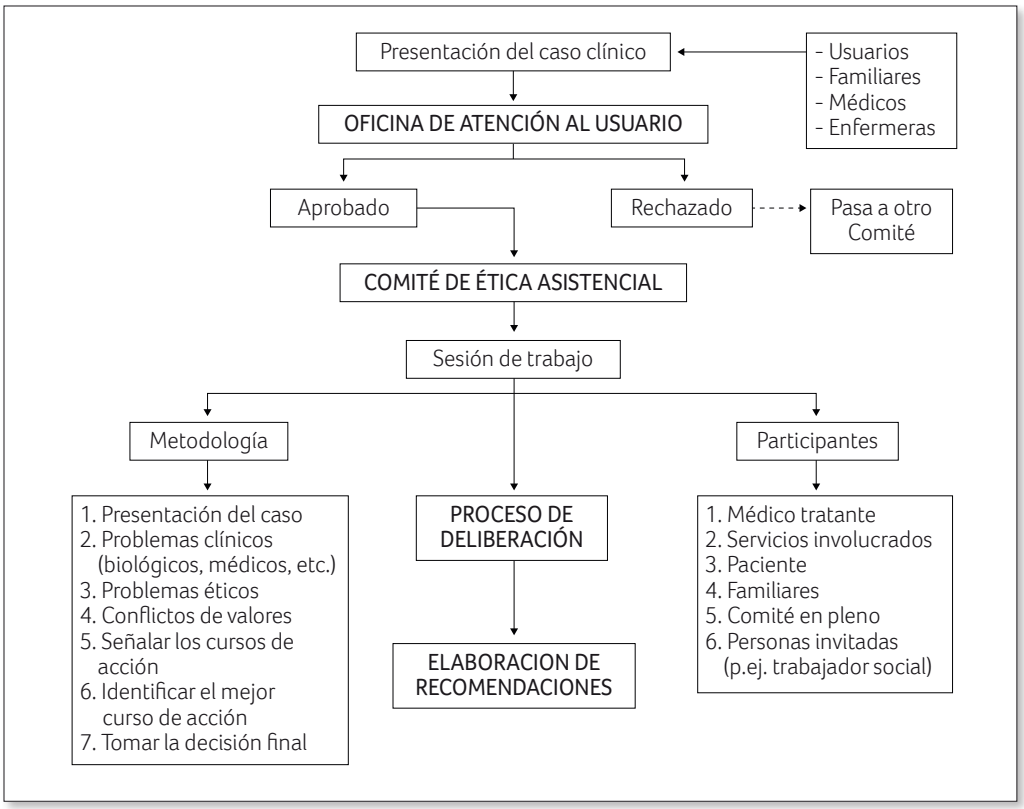

FIGURA 2.

Procesos y procedimientos

Véase la figura 2.

COMITÉS DE ÉTICA DE LA INVESTIGACIÓN

Momentos clave en la constitución de los Comités de Ética de la Investigación:

- 1946. Se crea el primer código de ética de la investigación con seres humanos como reacción a las investigaciones realizadas durante el régimen nazi: el Código de Nüremberg. Este código establece que el consentimiento voluntario del sujeto sometido a investigación es absolutamente esencial.
- 1948. Se elabora el primer ensayo clínico con un grupo de control seleccionado correctamente al azar que permitió concluir que la estreptomicina comparada con el reposo en casa, reducía la mortalidad y mejoraba la evolución radiológica de las lesiones pulmonares en tuberculosos.
- 1953. Los Institutos Nacionales de Salud de Estado Unidos estipulan que toda investigación que se llevara a cabo en sus clínicas de Bethesda (Maryland) y que involucrara a seres humanos, debería ser antes aprobada por un Comité responsable de su protección.

- 1962. Se establecen los conceptos básicos de un ensayo clínico controlado por el Dr. Austin Bradfort Hill. Se descubren los eventos adversos teratogénicos de la Talidomida y se exige a la industria farmacéutica que, antes de obtener el registro de comercialización de un medicamentos, demuestren científicamente su seguridad y eficacia.
- 1964. La Asociación Médica Mundial adopta la Declaración de Helsinki, en la que se efectúa la distinción entre experimentación terapéutica y experimentación sin finalidad terapéutica, y establece el principio de que no debe permitirse ningún experimento en el que el riesgo del paciente esté por encima de su beneficio. De esta Declaración hay varias revisiones en 1975, 1983, 1989 y 2000.
- 1966. El Doctor Henry Beecher publica el articulo "Ethics and clinical research" en el que denuncia que 50 protocolos de investigación poseen fallas éticas principalmente en la poca información que se da al paciente sobre los posibles riesgos y beneficios esperados.
- 1971. El Departamento de Salud, Educación y Bienestar de Estados Unidos publica una guía institucional para la protección de sujetos humanos, que ha de ser acatada por las instituciones que pidan financiación estatal.
- 1972. Se denuncian las fallas éticas en el estudio sobre la evolución natural de la sífilis en Tuskegee (Alabama). El estudio había comenzado en 1932 con 400 pacientes de raza negra para observar la evolución natural de la enfermedad, a pesar del advenimiento de la penicilina por los años 40. El estudio continuó hasta que se tuvo conocimiento del caso en 1972.
- 1974. El Congreso de los Estados Unidos aprueba el *National Research Act* por el se crea la *National Commission for the Protection of Human Subjects of Biomedican and Behavioral Research* con la misión de recomendar directrices éticas para la investigación que se deberían poner en práctica en forma de regulaciones.

Funciones

Véase la tabla 2.

Procesos y procedimientos

Véase la figura 3.

COMITÉS DE ÉTICA DE LAS ORGANIZACIONES SANITARIAS

Al comienzo, los Comités de Ética asistencial de los hospitales norteamericanos se encontraron con que al analizar los problemas éticos de los casos clínicos, había asuntos que superaban el ámbito privado del caso y se internaban en el terreno de la organización y funcionamiento del servicio de la institución. Por ejemplo, el problema puntual del incumplimiento de un médico con el manejo de consentimiento informado se convirtió también en el problema de la escasa organización al respecto del servicio clínico en donde se produjo en incumplimiento.

De esta forma, los comités de Ética fueron descubriendo que, además de abordar los casos puntuales de dilemas éticos médico/paciente, debían preocuparse por hacer una Bioética de corte más preventivo y estructural, proponiendo protocolos de la acción ética y

TABLA 2. Comités de Ética de la Investigación.

1. Evaluará la idoneidad del protocolo en relación con los objetivos del estudio, su eficiencia científica (la posibilidad de alcanzar conclusiones válidas, con la menor exposición posible de sujetos) y la justificación de los riesgos y molestias previsibles ponderadas en función de los beneficios esperados para los sujetos y la sociedad
2. Evaluará la idoneidad del equipo investigador para el ensayo propuesto
3. Evaluará la información al paciente y el consentimiento informado sobre las características del ensayo que se dará a los posibles sujetos de investigación, o en su defecto, a su representante legal, la forma en que dicha información será proporcionada y el tipo de consentimiento que va a obtenerse
4. Comprobará la previsión de la compensación (pólizas) y tratamiento que se ofrecerá a los sujetos participantes en caso de lesión o muerte atribuibles al ensayo clínico y del seguro o indemnización
5. Conocerá y evaluará el alcance de las compensaciones que se ofrecerán a los investigadores y a los sujetos de la investigación por su participación, así como el presupuesto total de la investigación
6. Realizará el seguimiento del ensayo clínico desde su inicio hasta la recepción del informe final
7. Recibirá de los sujetos de investigación o de cualquier otra parte, denuncias de abusos o notificación de los hechos adversos que puedan alterar el curso normal del estudio, decidiendo por la continuidad, modificación o suspensión de la investigación, debiendo, si e necesario, adecuar el término del consentimiento

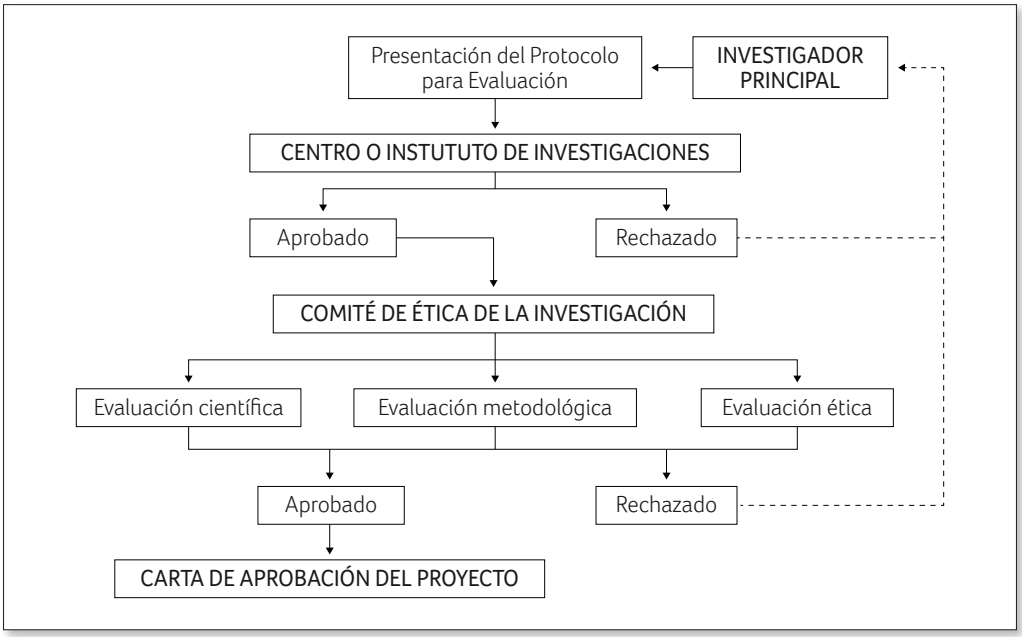

FIGURA 3.

TABLA 3. Comité de ética de las organizaciones sanitarias.

1. Se ocupa de la deliberación sobre los valores relevantes para una organización de la salud, que son las que la definen internamente y la diferencian externamente, así como la aplicación a todos los procesos (clínicos, investigativos y de gestión) que realiza dicha organización con relación a las personas o grupos de personas que influyen o son afectadas por ella en sus intereses, en orden a convertir dicha organización en una institución de excelencia

formando a los profesionales en las tomas de decisiones éticas. De esta manera, a la misión clásica e inicial de los comités fueron añadiéndose estas otras: realizar protocolos y capacitar en Bioética. Inconscientemente, los comités de Ética hospitalaria estaban dando el paso de la Bioética clínica a la Ética organizacional.

Se entiende por Ética de las organizaciones sanitarias las partes de la Bioética que se ocupan de la deliberación sobre los valores relevantes para una organización de la salud, que son las que la definen internamente y la diferencia externamente, así como de su aplicación a todos los procesos (clínicos y de gestión) que realizan dicha organización con relación a las personas o grupos de personas que influyen o son afectadas por ella en sus intereses *(stakeholders)*, en orden a convertir dicha organización en una institución de excelencia.

Todavía en el medio de la salud en países como Colombia no se ha dado el salto de los comités de Ética hospitalaria a los comités de Ética de las organizaciones sanitarias, puesto que se considera que los comités de Ética asistencial deben ser autónomos y no tomar decisiones vinculantes, pues muchos creen que perderían su transparencia. Al aceptar el reto de transformarse en comités de ética de las organizaciones de la salud su vinculación y relación con las directivas de las instituciones de salud debe ser mucho más fuerte, llegando a convertirse en instancias que dependan en su totalidad de la administración, perdiendo algo de su autonomía.

Funciones

Véase la tabla 3.

Procesos y procedimientos

Cada institución deberá organizar su propio proceso y procedimiento para el funcionamiento de este comité.

COMITÉS NACIONALES DE BIOÉTICA

Las Comisiones Nacionales de Bioética son instituciones creadas para dar respuesta la demanda creciente de ética por los poderes públicos, la comunidad científica y médica así como la opinión pública, ante las situaciones creadas por el progreso que pueden afectar la salud, perturbar la economía, la demografía, el derecho y la tradición. Estos comités se ca-

TABLA 4. Comisiones Nacionales de Bioética.

1. Formular y presentar al Gobierno documentos que aborden de manera amplia el análisis sobre los interrogantes éticos que plantean los avances científicos y tecnológicos cuando involucra a seres humanos y formule recomendaciones que concilien la libertad de investigación con el respeto a la dignidad humana
2. Ser órgano asesor del Gobierno Nacional en lo que tenga que ver directa o indirectamente con los asuntos éticos derivados de la investigación científica
3. Ofrecer consejo y formular recomendaciones al Gobierno en asuntos relacionados con las implicaciones éticas de la intervención e investigación en el genoma humano; clonación, investigación biomédica; fertilización *invitro,* extracción y trasplante de órganos y tejidos y xenotrasplantes, con individuos y comunidades, en especial las que se realicen o pretendan realizarse en minorías étnicas o raciales, menores de edad, discapacitados, cadáveres y animales
4. Estudiar y elaborar informes o dictámenes sobre los problemas éticos que surjan en la actividad de los Comités Bioéticos Clínicos de investigación y asistenciales de las instituciones hospitalarias del país y que sean de interés o ámbito nacional

racterizan por ser de naturaleza consultiva, por abordar múltiples aspectos; están integrados por personalidades con autoridad moral, buscan respuestas a los interrogantes planteados por la sociedad y ayudan a los gobiernos a establecer responsabilidades.

Se puede decir que los comités de Bioética han pasado por tres etapas definidas:

1. **Etapa de instauración: de 1970 a 1982.** Se constituyen comités nacionales de carácter temporal y *ad hoc,* en general con gran orientación jurídica y sus principales temas giraron en torno a los proyectos de investigación, ética de la diálisis y los trasplantes, aspectos éticos del final de la vida y los dilemas éticos de las técnicas de reproducción asistida.
2. **Etapa de expansión de los comités: de 1982 a 1994.** Se instaura en Francia de Comité *Consultatif National d´ Ethique pour les Sciences de la Vie,* constituyéndose en paradigma de los comités nacionales de Ética en todo el mundo. Los principales temas de estudios fueron entre otros las implicaciones éticas de la ingeniería genética, la Medicina predictiva y la Farmacogenética, el estatuto del embrión y la utilización del tejido fetal, la confidencialidad de los datos genéticos y de las pruebas del VIH, la aplicación del consentimiento informado en los estudios clínicos y el dilema de la despenalización y legalización de la eutanasia.
3. **Etapa de la extensión de comités: de 1995 hasta nuestros días.** La influencia de la globalización hace surgir la necesidad de comités que sobrepasen las fronteras de los países y se constituyan comités supranacionales de Ética. Se están desarrollando temas como la clonación, el genoma y la Medicina perfectiva, las terapias con células embrionarias, los xenotrasplantes, la muerte digna y la limitación del esfuerzo terapéutico, y la experimentación en países vulnerables.

Funciones

Véase la tabla 4.

La tabla 5 muestra los diferentes comités nacionales y supranacionales.

TABLA 5. Comités nacionales y supranacionales.

Estados Unidos	The president`s Commission (1980-1983) The National Bioethics Advisory Commission (1995-2001) The president`s Council on Bioethics (2001)
Gran Bretaña	The Peerl Report (1972) The Warnock Report (1982) Advisory Committee on Genetic Testing (1996) Human Genetics Commission (1999)
Australia	The National Health and Medical Research Council The Australian Law Reform Commission (1975) The National Bioethics Consultative Committee (1988) The Australian Health Ethics Committee (1991)
Canadá	The Law Reform Commission of Canadá (1971-1992) The National Consultive Medical Research Ethics Committee (1989)
Holanda	The Central Commission on Research Involving Human Subjects
Noruega	Comité Nacional de Ética para la investigación (1988)
Finlandia	Comité Consultatitif National d`Ethique pour les Soins de Santé
Suecia	Comité Sueco de Ética Médica (1984)
España	Comité sobre Medicamentos y ensayos Clínicos (1984) Comité Central de Deontología Comisión Nacional sobre Reproducción Asistida (1995)
Francia	Comité Consultatif National d`Ethique pour les Sciences de la Vie (1993)
Italia	Comitato Nazionale per la Bioetica (1989)
Portugal	Conselho Nacional de Ética para as Ciencias da Vida (1990)
Bélgica	Comité de Ética del Fondo de la Investigación Científico-médica Comité Consultatif National de Bioéthique (1993)
Suiza	Comité Central de Ética Médica (1975)
Alemania	Comisión Benda (1985)
Consejo de Europa	Comité Directeur de Bioethique (1991) Convenio sobre la Protección de los Derechos del Hombre y la Biomedicina (1997)
Unesco	Comité Internacional de Bioética (1993)
Europa	European Group of Ethics (1997)
Japón	The Science and Technology Council's Bioethics Committee (1998)
Israel	The National Council for Research and Development
Méjico	Comisión Nacional de Bioética
Colombia	Comisión Intersectorial de Bioética
Argentina	Comisión Nacional de Ética Biomédica

Procesos y procedimientos

Cada institución deberá organizar su propio proceso y procedimiento para el funcionamiento de este comité.

CONCLUSIONES

Existe un gran desconocimiento en Latinoamérica sobre la importancia y el funcionamiento de los Comités de Bioética. Es labor de las universidades e instituciones de salud promover su implementación y apoyar todo tipo de esfuerzo para una mejor atención a los usuarios (pacientes), que en últimas son el quehacer de la práctica asistencia, la práctica investigativa y la práctica organizacional.

RECOMENDACIONES

- Cada institución debe definir y adecuar los propios objetivos y funciones de los Comités, de acuerdo con las necesidades locales de cada país.
- Procurar organizar formas de capacitación continúa de los miembros de cada Comité, otorgando además facilidades para que algunos de los miembros alcancen estudios de postgrado en Bioética.
- Procurar que los integrantes de los comités formen un grupo interdisciplinario y de equilibro entre hombres y mujeres.
- Establecer una forma de trabajo sistemático, con periodicidad y reglamentación de reuniones.
- Registrar la experiencia de los Comités, evaluar periódicamente sus actividades, métodos y criterios.
- Precisas con la dirección de la institución los recursos necesarios para el desarrollo de las funciones de los Comités.

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Análisis de los elementos éticos que intervienen en la praxis clínica

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INTRODUCCIÓN

La evolución de la Biomedicina ha propiciado la aparición de nuevos problemas éticos que se convierten en tema de debate público. A la vez, se plantean dilemas que exigen cierta reflexión antropológica que no es corriente hallar en los planes de estudio de Medicina, Enfermería, Fisioterapia o Farmacia[1]. El resultado es que la profesión médica se halla abocada a tomar decisiones que a veces superan sus competencias, y se suele derivar hacia los profesionales del derecho. La aparición de los mismos comités es ya un reflejo de esa denuncia: no es posible ni es bueno legislar sobre todo, porque no es la función de las leyes y una sociedad judicializada aniquilaría cualquier iniciativa, vulneraría la responsabilidad individual y colapsaría el sistema. Hay que recordar que los CEA son creados para analizar y asesorar en la resolución de los posibles conflictos éticos que se producen durante la práctica clínica en las instituciones sanitarias, a consecuencia de la labor asistencial, y cuyo objetivo final es mejorar la calidad de dicha asistencia. Aun así, la cuestión queda sin resolver. A medida que la misma dinámica tecnológica irrumpe en la práctica clínica y se extiende la atención sanitaria a todos los ámbitos de la sociedad, los dilemas y decisiones morales por parte de los profesionales sanitarios y los comités éticos son cada vez más difíciles de resolver desde el punto de vista técnico[2].

Todo ello impulsa a buscar herramientas y metodologías de decisión que faciliten la labor de los profesionales y de los comités, obligando a una reflexión interdisciplinar, con el objetivo de proteger, sobre todo, al paciente y al personal sanitario en las acciones controvertidas que se dan en la práctica. En ocasiones, se ha tratado de asimilar la toma de decisiones ético-clínicas a los procesos que se siguen en el ámbito empresarial o en los ordenamientos judiciales[3]. Pensamos que son planteamientos valiosos pero pueden resultar reductivos en el momento de aplicar decisiones a un paciente, como se reveló en el caso Quinlan, y que dio lugar al nacimiento de los Comités Éticos. Por ello trataremos de estructurar un sistema de razonamiento que compatibilice la agilidad en la toma de decisiones y las bases antropológicas más elementales de la ética clínica.

DESCRIPCIÓN

El esquema de trabajo se estructura a partir del principio de precaución en su sentido más amplio[4], es decir, lo que en ética filosófica denominamos prudencia. Según la tradición

platónica, la prudencia es una virtud que gobierna las demás virtudes, que a su vez regulan las actuaciones pertinentes para dirigirlas a su fin específico. Esta línea de pensamiento se ha ido desplegando en occidente, de modo que la prudencia se considera una categoría bien asumida y entendida por toda la sociedad. Se le reconocen tres elementos o actos: el consejo (recibir información y deliberar sobre la acción que se evalúa); el juicio (valoración de los elementos referidos al bien de la actuación, decidiendo la actuación más correcta); y el imperio (determinación de obrar sobre lo juzgado como prudente). La prudencia, en fin, constituye la base argumental del Principio de Precaución, el cual extiende su aplicación desde el mundo de la ecología hasta la geopolítica, pero que cada vez adquiere mayor preponderancia en el ámbito sanitario[5]. Con este referente, es posible elaborar un esquema de trabajo que constituye la base del Principio de Precaución aplicado a la praxis clínica. Su reformulación permite distinguir tres fases en el momento de tomar decisiones en el ámbito ético-sanitario: diagnóstico, decisión y ejecución.

Diagnóstico

Es la formulación concreta del problema ético en la situación que se estudia. No se debe confundir con el diagnóstico clínico, que aquí resulta secundario. Aquí es importante detectar la dimensión moral del problema, algo que puede resultar difícil a muchos profesionales no versados. Se busca conocer la realidad del problema planteado, acudiendo a la experiencia acumulada y las decisiones tomadas por otros. Esta primera fase se subdivide en otras tres:

1. **Referencia a los principios o valores éticos involucrados:** aunque pueden variar según la experiencia o cultura de cada profesional, suelen coincidir en sus aspectos más generales. Se debe hacer referencia al Principio de no maleficencia, entendida como no hacer daño y respetar la vida y la integridad del ser humano. También se debe tener en cuenta el Principio de beneficencia, es decir tratar de producir el bien en el paciente, teniendo en cuenta el principio de proporcionalidad terapéutica. Así mismo, se debe citar el principio de autonomía, entendida como la libertad responsable para aceptar o rechazar un tratamiento. Y el principio de justicia, que tiene en cuenta a su vez el principio de solidaridad entre los componentes de la sociedad.
2. **Análisis de las competencias del paciente o sus representantes.** Esto incluye la identificación de los valores y prioridades del paciente, el grado de competencia que tiene el paciente para participar en la toma de decisiones, la identificación de representantes legales, y la red de apoyo social-familiar ante la situación provisional del paciente.
3. **Análisis de la información científico-clínica éticamente relevante.** Se concreta en conocer bien la certeza de los diagnósticos, las alternativas terapéuticas con sus respectivos beneficios y riesgos, los pronósticos de sobrevida basado en la evidencia, y los costos (físicos, psicológicos, espirituales, económicos, etc.).

Decisión

Se quiere una solución y se pondera el equilibrio de los elementos positivos y negativos, la deliberación de alternativas, así como la elección de la solución más justa posible. Esta segunda fase también se subdivide en tres:

1. **Intención.** Dilucidar qué es lo que pretendo con mi acción (orientación inicial del comportamiento), entendida como una mejora de la situación actual. Es el motivo último de la

actuación, lo cual supone, en ocasiones, abstraerse de soluciones tópicas, premeditadas o políticamente correctas.
2. **Deliberación de las alternativas.** Búsqueda de los medios para alcanzar el fin, teniendo en cuenta la jerarquía de esos medios. También se barajan conceptos como el doble efecto, el mal menor o la cooperación material. Es la parte más creativa del proceso, donde se barajan todas las posibilidades y alternativas que se puedan recoger.
3. **Elección.** Tomar una decisión teniendo en cuenta el principio de precaución, donde la prudencia alcanza su cenit, a la vez que se rechazan las restantes alternativas, con los argumentos y valoraciones pertinentes.

Ejecución

Consiste en la determinación y concreción de la decisión tomada, la implementación de la alternativa elegida, especificando las circunstancias y asumiendo las posibles consecuencias, así como estableciendo el seguimiento de la actuación, de la cual se extraerán nuevas experiencias. La subdividimos en dos fases:
1. **Concretar las circunstancias** (modo, lugar, tiempo, etc.).
2. **Evaluación de los resultados** (las consecuencias, si se conocen).

DISCUSIÓN

El esquema sigue un orden lógico e incorpora la dinámica procesal, frecuente en los procedimientos jurídicos, al mundo sanitario, siendo las leyes sanitarias y los protocolos únicamente el marco de referencia para tomar decisiones. Pero son los principios de ética médica y la conciencia moral de los miembros del comité los que elaboran el dictamen. Esto hace que el mismo caso pueda derivar en direcciones opuestas según la composición del comité, pero las bases de discusión serán claras y sencillas de consensuar[6].

Esto se ha podido comprobar con frecuencia a la hora de plantear los casos o dilemas éticos a estudiantes del ámbito sanitario. En el curso del debate, la coincidencia no es lo esperado, pero el debate se hace más fluido[7]. Lógicamente, los puntos conflictivos no se centran la deliberación de tratamientos alternativos o en su ejecución, si no en los principios a aplicar. Por eso se parte de un conocimiento más detallado de elementos de ética general, que incluya los conceptos como el de "bien del paciente", "autonomía", "dignidad", "justicia", "vulnerabilidad", "integridad" o "verdad"[8]. A partir de estos elementos se puede debatir sobre los principios a seguir, tanto si se utilizan los principios de Beauchamps & Childress como los principios elaborados por la Unesco en 2006.

La evaluación de las competencias del paciente obliga a tener en cuenta su situación subjetiva (lo que el paciente piensa y siente sobre su situación) y su situación objetiva (los condicionantes individuales o sociales, observables por otros), que a veces facilitan la resolución del caso. Del mismo modo, el conocimiento de aspectos clínicos que afectan a la dimensión moral del problema, especialmente los costos generados, pueden ayudar a perfilar con precisión la solución.

En el ámbito de la Intención, el aspecto más problemático es la dispersión de los fines, es decir, "qué es lo que se pretende". Aquí el debate suele reflejar los principios que sustentan

cada opinión, pero concuerdan a la hora de buscar alternativas que mejoren la situación actual. La elaboración y exposición de alternativas que traten de alcanzar la intención buscada resulta la parte que mayor esfuerzo requiere, ya que cada una exige reflexión y argumentación. La elección de la decisión más correcta será la que mejor asuma los puntos descritos en el diagnóstico.

En ocasiones, una decisión ideal desde el punto de vista ético puede naufragar a la hora de aplicarla, por no haber sabido concretar su implementación. De ahí la importancia del último aspecto del esquema. Todas las circunstancias deben ser materializadas, especialmente si se trata de elaborar un dictamen ético. Posiblemente sea la fase más práctica de la decisión y por tanto, más laboriosa y difícil, pero es importante exteriorizarla para evitar los síndromes burocráticos que pueden acompañar estos procesos. Del mismo modo, el seguimiento de la decisión tomada suele ser tediosa, pero resulta especialmente instructiva a la hora de mejorar la dinámica de la toma de decisiones en el ámbito clínico.

CONCLUSIÓN

La estructuración de dilemas éticos en el ámbito de la salud resulta altamente conveniente para la resolución de casos conflictivos, tanto en situaciones restringidas al ámbito individual del profesional sanitario como en el ámbito de los comités asistenciales. El esquema permite rigor y orden a la hora de decidir, establecido sobre conceptos más elementales de la ética. Entre ellos, adquiere especial relevancia el ejercicio de la prudencia clínica y el principio de precaución. Las tres fases del esquema presentado se asocian, a diferente escala, al mismo proceso empleado en la toma de decisiones en niveles individuales.

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What does Research Ethics Committees know about their independence and the rules of good clinical practice?. The example of Valencian Autonomous Community

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BACKGROUND

According to under of Regulation (EU) No 536/2014 conditions:

- 'Ethics committee' is an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purposes of this Regulation, taking into account the views of laypersons, in particular patients or patients' organizations.
- And "Good Clinical Practice" (GCP) is a set of detailed ethical and scientific quality requirements for designing, conducting, performing, monitoring, auditing, recording, analysing and reporting clinical trials ensuring that the rights, safety and well-being of subjects are protected, and that the data generated in the clinical trial are reliable and robust.

And because the sponsor and the investigator of a clinical trial shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of GPC, it is essential that ethics committees and their members be independents and known the guidelines on GCP.

OBJECTIVE

To record Research Ethics Committees (REC) knowledge about their independence and the rules of good clinical practice, in our Valencia Community, Spain.

METHODS

We elaborate and send to fill a check-list type questionnaire. They have to complete a questionnaire for 22 REC that have been adhered to Spanish Medicines and Medical Devices Agency collaborative memorandum following regulations. The questionnaire had 4 parts: general data, GPC, REC independency and SWOT analysis to find strengths and weaknesses, and the opportunities and threats).

RESULTS

A total of 6 (27%) REC and 12 members completed the questionnaire. The number of members per responding REC was between 13 and 22. The number of clinical trials evaluated as REC of reference in 2016 was 0-2.

Regarding the knowledge o f GCP the majority of members refer to know the GCP principles but they do not identify which is the last review. With respect to the GCP training, most of them have accredited training due to their role as investigators and also consider that it is important.

In reference to the independence, they understand that independence means specially liberty and then lack of interest and that the independence is with respect to sponsor, investigator, centre and foundation. They affirmed that the independence is achieved by means of written documents (personal declaration and Standard Operating Procedures of the ERC). They interpret that are financial and personal conflicts of interest. Members say never have feel their independence coerced.

CONCLUSIONS

In our region, ERC members feel that GCP training and independence are important. We can be concluded that there is necessary a specific, continuous and quality training for ERC members.

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Building Bridge to International Biomedical Research: S.D. Asfendiyarov Kazakh National Medical University REC's Experience

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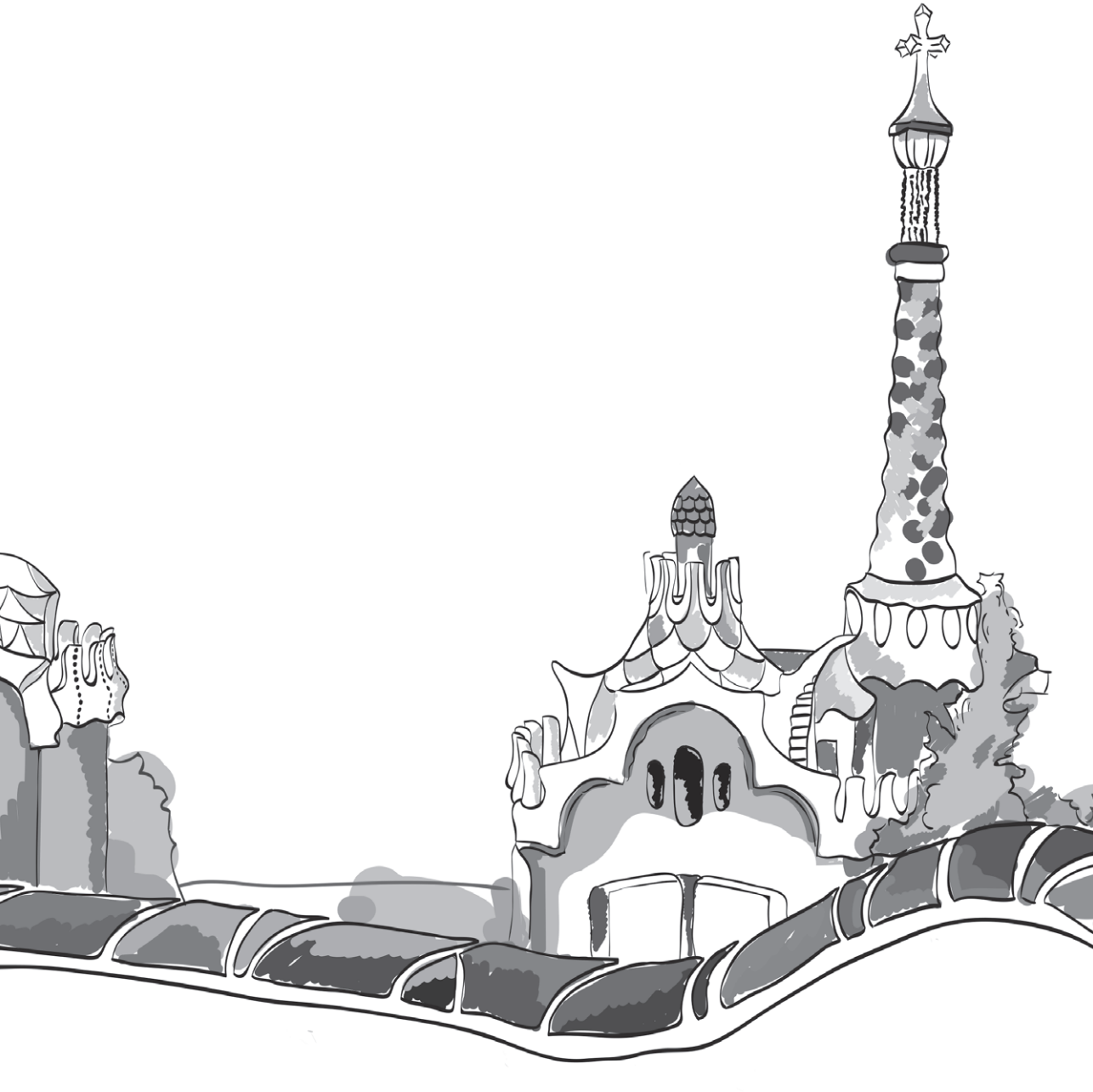
ABSTRACT

Despite of that international research collaboration is growing rapidly international academic institutions still have problem with expanding their research to Kazakhstan. Lack of research ethics capacity conforming international research ethics requirements at institutions involved in biomedical research caused a problem in republic.

Communication is aimed to share experience of S.D. Asfendiyarov Kazakh National Medical University (KNMU) Local Ethics Commission (LEC is equivalent of REC) in problem solving.

International, national and local programs achievements contributed to KNMU LEC success. First, it is Kazakhstan 2050 Strategy calling for widespread economic, political and social reforms for reaching a position among the top 30 global economies by 2050. To contribute the Strategy the KNMU made goal to become competitive Research University. KNMU management team headed by rector taking responsibility for science development and possible consequences developed in KNMU biomedical technologies on society made a goal to improve research ethics review system to meet international ethical standards. Within Kazakhstan Ministry of Education and Science program № 020 "Attracting foreign experts" KNMU invited alumna of Post Graduate Web Based Advanced Certificate in Research Ethics for Central and Eastern Europe (RE CEE), Union Graduate College (UGC) and Vilnius University, sponsored by National Institutes of Health-Fogarty International Center (With US National Institute of Environmental Health Sciences, National Heart, Lung, and Blood Institute, National Institute of Drug Abuse) and MSc Bioethics Program, UGC, Mt Sinai School of Medicine, Schenectady, New York, USA, sponsored by National Institutes of Health-Fogarty International Center for visiting professorship. Alumna was involved in both research ethics teaching and work as KNMU LEC vice-chair. During visiting professorship period 2012-2016, University Research Ethics Capacity Building Program successfully implemented. KNMU enjoys system of research ethics review meeting international ethical requirements showing increasing in number of research projects application at LEC in more than 7,78 times. Number of international biomedical research project applications also increased. From no or one project in 2009-2013 years, it increased to four in 2014, four in 2015, and three in 2016.

Thus, KNMU LEC successfully built bridge to international biomedical research due to wise and rational use of international, national and local programs achievements by KNMU leaders. Involvement of alumna of Post Graduate Web Based Advanced Certificate RE CEE and MSc Bioethics Program, UGC, Mt Sinai School of Medicine as visiting professor was essential for KNMU to become competent partner in international biomedical research.



CONFERENCIA DE CLAUSURA

The future of RECs, perspectives and hopes

Prof. Elmar Doppelfeld
Chair of EUREC

Thank the organizers for the invitation moreover for the charge to speak on "The future of RECs, perspectives and hopes".

I prepared this statement during the days of our congress to keep the most actual stand of our discussions. The contribution therefore may be not of the highest performance.

In the light of the panels we heard yesterday it would be too ambitious or even foolish to say on the future of RECs anything more than: I do not know. Any kind of prediction would be similar to predictions based on the observation of flying birds as carried out e.g. by the augurs in ancient Rome. I restrict my presentation to some thoughts on RECs and on their general mission. This is in few words: protection of research participants and ensuring a qualified medical research in the frame of ethical norms. Such research is necessary in the interest of present and future patients: improvement of treatment and avoiding any procedure which might be useless and/or harmful for the person concerned. This principle can be found already in the corpus hippocraticum.

The involvement of persons into such research is linked with risk and burden, and we cannot predict meaningful results for the person concerned, for the group or for the improvement of knowledge. Research is linked to interventions. In the very past research on persons was carried out in the course of interventions justified by the intention to care. Experience for further treatment and data were gained as side effect. Starting in the enlightenment time the justification for physical interventions with the only aim to gain knowledge was accepted. This lead to experimentation on human beings starting in the 19th century. In the same period the question of ethical and legal justification of these experiments was raised.

Today we distinguish between physical and non physical interventions: the ones violating the integrity of the body, the others using data or stored biological material for research and by that interfering with fundamental rights and freedoms. The RECS are placed in a position like a mediator: justified research on the one hand, on the other hand protection of autonomy, dignity, identity and well-being of the involved person. To which extent may these principles touched or even restricted in favour of a common good: Healthcare and/or knowledge? The Belmont Report as an example summarizes the basic principles: autonomy, beneficence and justice, which are fruits of the discussion on going since the 19th century.

The mission of RECs can be defined shortly as review of a research project under ethical perspectives. The scientific quality and the conformity with law as preconditions must be

given and should be assessed by the REC or by other competent bodies. RECs are review boards performing the ethical review in the light of given and accepted ethical principles in a society including cultural factors. RECs are not entitled to develop "new ethics", by intellectual basic work or by combination of different schools of ethics. In the past a change of the name to "moral review boards" or "simply decision seeking bodies" to be more appropriate was discussed – RECs stays as you know. Even if not legitimated to introduce new ethics the RECs may show the way to the application of ethics for new research fields like research including children as we learned yesterday. Main responsibility is the protection of principles as laid down e.g. in the Belmont report. These principles need interpretation, which may vary from committee to committee. It is a duty of RECs to ensure that these principles are applied in a manner to fulfil the protective aims. The free informed consent as such must be kept but must be sought in a manner, that the intention "free decision on valid information" is safeguarded.

RECs should work to improve the awareness of researchers and sponsors on these principles and to encourage them to look for inherent ethical problems in general and specifically in a specific research project. REC could do this by open conferences with third parties and by discussions e.g. with the applicants of a submitted project. RECs should foster these initiatives. Even after 4 or more decades following the first formation of RECs applicants very often do not specifically consider ethical implications of their projects, just saying or writing, that the DoH is followed, which of course is only a compilation of ethically based principles but not itself an "Ethic".

The question raises on the reliability of world wide accepted ethical norms. Example autonomy with different interpretations in different countries or regions! Is there a uniform ethics which could serve as the basis for discussions and specifically decisions of RECS? I think at least not yet.

The impact of RECs activities in other, non ethical fields is better: the scientific quality of submitted projects –structure, methodology, justification of envisaged research etc. has improved– RECs work like a filter. The understanding of legal conditions for research may also be deeper than before. However: still very often research as such is claimed as the decisive justification for a project prevailing all other points.

The RECs should become more a partner in discussion on all these relevant fields, they should serve as adviser before any kind of submission: learning from each other and improving the quality of projects to be submitted. RECs should be a discussion partner for researchers, and should not feel as an authority even if their decision brings them next to an authority. Specifically RECs should improve the interest of researchers on ethics, the different steps for an approach and the different existing ways to come to a conclusion on ethical issues. Ethics are accepted in the public, everybody, namely politicians are in favour of ethics. but administrative frames are and seem to become more and more restrictive for the procedure of RECs, so that a duly qualified evaluation is difficult as we heard by several presentations concerning the Drug Regulation.

RECs and their networks on national level or as EUREC on European level should contribute to public debates on ethics in research – medical or other research involving human beings with the intention to prevent any further marginalisation of ethics. The trust of the public in research could be improved. Some specific aspects:

- **Composition and influence:** Independence of RECs as bodies and of the members is the condition for performing the protective mission – protective for participants including the researchers and protective for the quality of research.
  Multidisciplinary composition, proven specialists in ethics, law, theory of medical research, these specialists should be specifically interest in the responsibilities of RECs and willing to take over this burden. Additional timely members as external experts are needed if required by the submitted project to be evaluated or a competent member has declared a conflict of interest in view of this projects. Nobody shall become member of REC if there is any conflict of interest – a general one by the background of that person, e.g. affiliation as an employee of a pharmaceutical company. Conflict of interest in a specific case: exclusion from decision making. No participation in decision making of persons directly or indirectly linked to the submitted project, the researcher is only admitted to answer questions and to clarify his proposal, decision are taken only by the REC in his absence. The quality of the REC in different fields must be given to avoid any unjustified critics against the REC. Actual problem: it becomes more and more difficult to find duly qualified persons to become members of a REC.
- **Affiliation of RECs:** Ministries, Research institutions, authorities in the health or other fields, public health bodies, "National Ethics Committees", RECs may also acting on private or commercial basis. Interests of establishing bodies: Academic reputation, funds for research, employment of staff, commercial interests or economical aspects like in a country or in a group of States like EU. These interests could but should never influence the RECs evaluation of the classical topics in view of a submitted research project:
- **Quality, law, ethics:** this evaluation should only be done by duly qualified members of the REC without any kind of conflict of interest or by external experts. Of course there may be different well justified conclusions. Quality and conformity with law may be assessed by different bodies as it is already the case in some European States. Question: to which extent can their decision be binding, for the RECs which are restricted to in these cases to the ethical assessment. Do they have a possibility to oppose to such an external assessment? To me the assessment of all the three points by one committee is preferable. Analytic ethics should have their place in the ethical evaluation, which is based on moral-regional convictions including so called cultural factors such as tradition, history or religion.
- **Laypersons** should be included in the decision having the same right to vote than other members, the questions and aspects of the project should be duly explained by competent members of the REC, not by external people. Who is a layperson, how long is a layperson a layperson? Kant and other philosophers: all men have a feeling for the good and for the bad and are therefore qualified to take a relevant decision without any kind of academic education. All members of a REC have the same ability to perform moral decisions, this is given to all human beings.
- **Legal character of votes:** binding or advice to the researcher? Depending on national legislation.
- **System of appeal:** not yet sufficiently solved. Can a court, can an authority overrule the vote of a REC?
- **Competence of RECs:** biomedical research as such or RECs specified to fields of biomedical research like e.g. urology. Since long time the establishing of RECs specifically competent

for dug and medicinal devices is discussed – in Germany until today refused namely by the pharmaceutical industry.

- **Extension of competence on non biomedical research:** staff, infrastructure and awareness of members with legal and ethical issues is given, of course appropriate participation of members who are familiar with the submitted project and duly assess it.
- **Data and stored tissue?** Role of RECs in on going discussion.

– **My hope:**
  - Independence of RECs as such and of its members is safeguarded, may be by legal guarantee.
  - Only RECs under public law to prevent the influence of different interests.
  - *Financing* by fees under public supervision or better by public financial sources like in Norway.
  - Administrative frame is necessary for procedure of the evaluation process, bylaws, safeguarding the rights of 3rd parties like applicant or sponsors. However they must not hinder a duly qualified evaluation of projects. taking into account that RECs are working with voluntary members, which are not clerks of the REC. Members of RECs should be working actively in their profession not to lose the necessary link.
  - *Harmonisation* of procedural aspects of application and evaluation.
  - *Respect for cultural factors in decision making.*
  - *RECs more open for discussion with applicants* namely ethical issues to improve the awareness of researchers for ethical implications.
  - *RECs* should be more willing and open for *discussion with the public* to improve the awareness of ethical implications.
  - *System of appeal* within the system of RECs.
  - *Courts decision* restricted to violations of administrative procedures and of obvious violations of fundamental rights and freedoms.
  - *Competence should not be altered:* research with physical intervention - basic research or clinical research - and research using data and stored biological material of human origin - diversities in the national systems, but RECs should be involved in any way.
  - *Other than biomedical research* involving human beings: RECs could be contribute by its experience, staff in addition to appropriate experts assessing the research project, like e.g. research in in agriculture and food.
  - *Closing remark:* I hope, that the existence and independence of RECs will be safeguarded, that RECs will be able to meet their responsibility with wisdom, justice and science.