CHILD CENTRED PAEDIATRIC RESEARCH: LEGAL AND ETHICAL CONSIDERATIONS UNDER THE NEW REGULATORY FRAMEWORK

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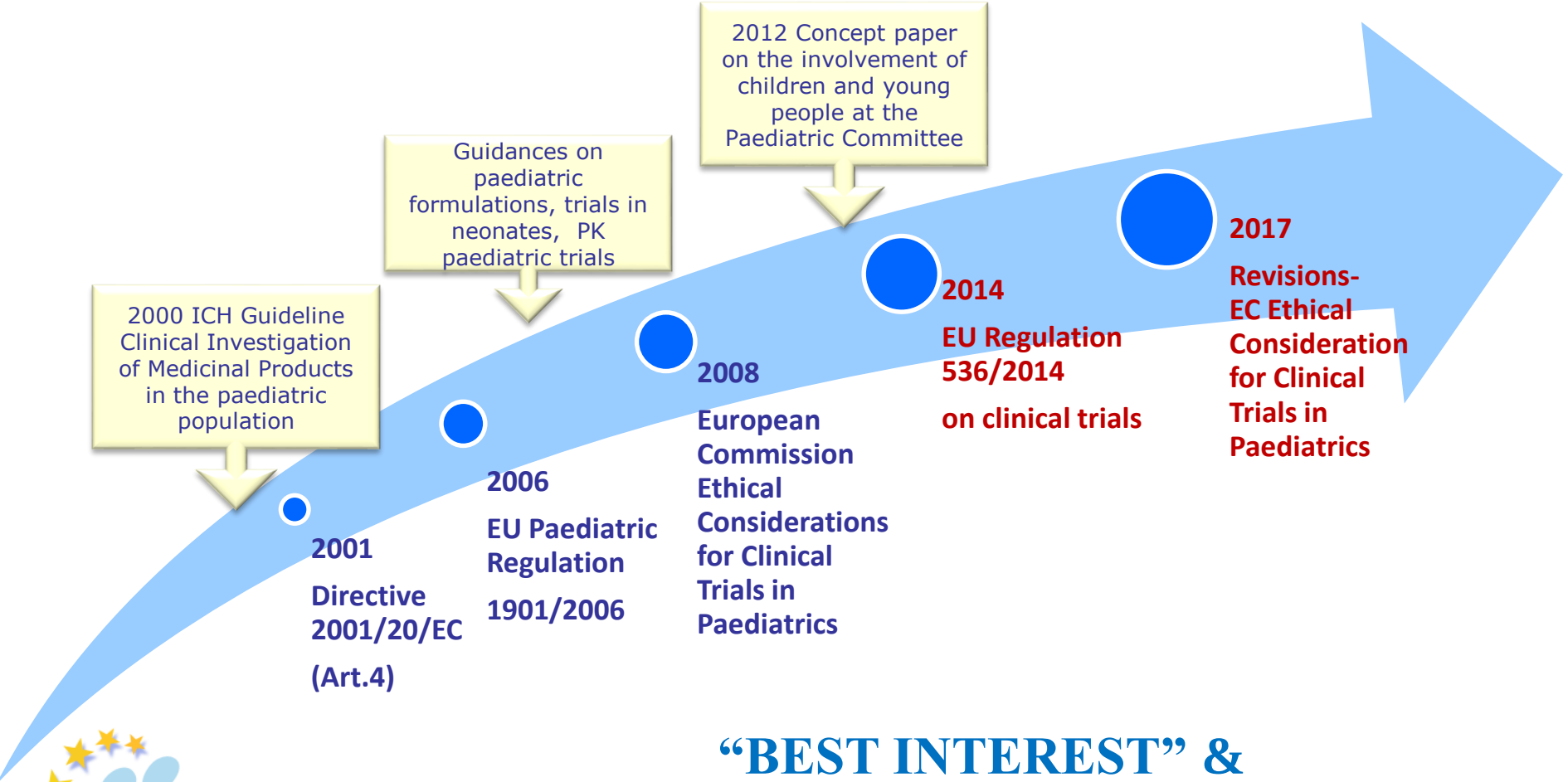
EU ETHICAL/LEGAL FRAMEWORK
Relevant for paediatric research



"BEST INTEREST" & "EVOLVING CAPACITIES" OF THE CHILD

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Despite requirements for conduct of clinical research according to ethical principles and taking into account paediatric peculiarities

- scientific value and validity
- favorable risk-benefit ratio
- informed consent procedure
- independent review (E.C.)
- respect of subjects
- fair subject enrollment and withdrawal

Specific issues under the new EU ethical/legal framework need clarification

- **Authorisation procedures/ Ethical assessment**
- **Risk/benefit assessment**
- **Respect of autonomy and involvement of children & parents**

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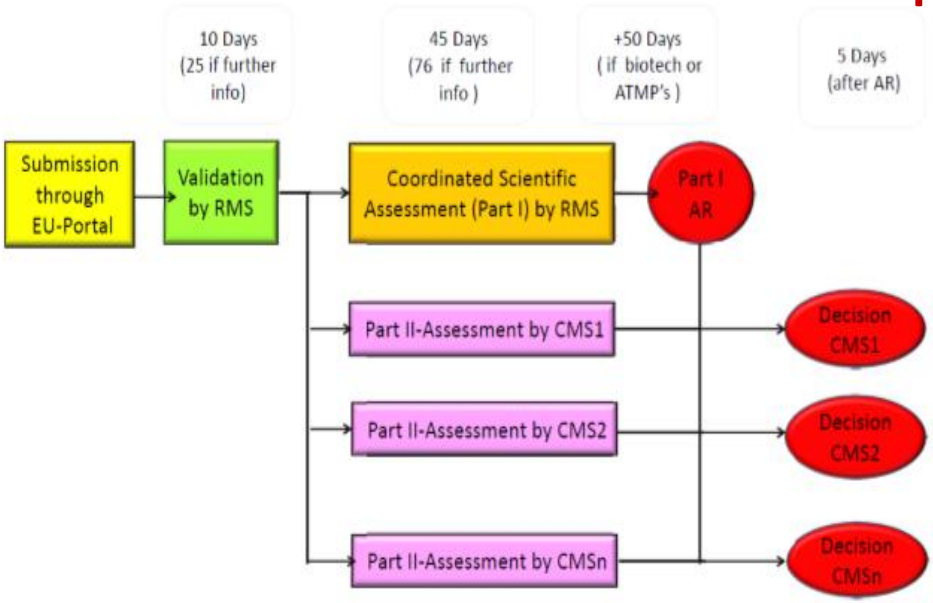
The new EU Regulation on CTs

Assessment report of part II



45 Days

- **26 days** assessment b
- **12 days** Coordin w phase by all MS
- **7 days** tion phase by RMS
- **5** ch Ms informs sponsor on the orisation of CT

Tacit Approval

- amount and type of data for Part II will remain governed by national laws
- each Member State has to determine which appropriate bodies (included Ethics Committees) will be involved in the assessment of the application within the timelines for the authorisation of that clinical trial as set out in this Regulation

Ethical review in "EC Ethical recommandations for paediatrics"

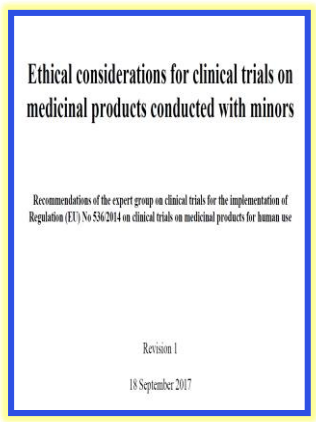
Ethics Committee paediatric expertise

- **permanent members of the Ethics Committee**

or

- **experts providing advice and consulted on clinical, ethical and psychosocial problems in the field of paediatrics**

2017 review: what is new?


Ethical considerations for clinical trials on medicinal products conducted with minors

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Revision 1

18 September 2017

- Paediatric expertise defined as a combination of education, training and some years of experience on many aspects of ethics, child development and psychosocial aspects, pharmacology
- Paediatric experts should be available for the assessment of the CTA/any substantial amendments
- ECs specialised in paediatrics could be considered where trials are complex (e.g. serious paediatric diseases, gene therapy)
- Some of layperson participating in the assessment of trial may be parents

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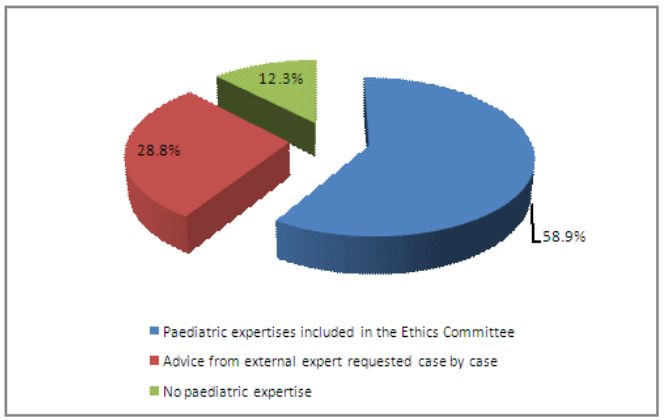
Inventory of Ethics committees at national level in Europe

1007 ECs / 29 countries

With different composition and functioning



Paediatric expertise usually represented by a paediatrician

90 ECs
D.M. 08.02.2013

COUNTRY	No. of ECs	Inhabitants (millions)	No. ECs / 1.000.000 inh.
Bulgaria	103	7.6	13.55
Iceland	3	0.3	10.00
Finland	25	5.3	4.72
Italy	270	60	4.50
Belgium	38	10.7	3.55
Austria	27	8.3	3.25
Spain	143	45.8	3.12
Ireland	13	4.5	2.89
Slovakia	13	5.4	2.41
UK	143	61.7	2.32
Latvia	5	2.3	2.17
Luxembourg	1	0.5	2.00
Malta	1	0.5	2.00
The Netherlands	32	16.4	1.95
Denmark	9	5.5	1.64
Estonia	2	1.3	1.54
Norway	7	4.7	1.49
Poland	54	38.1	1.42
Cyprus	1	0.8	1.25
Czech Republic	9	10.5	0.86
Sweden	7	9.2	0.76
Germany	54	82	0.66
France	40	64.3	0.62
Lithuania	2	3.3	0.61
Slovenia	1	2	0.50
Hungary	1	10	0.10
Portugal	1	10.6	0.09
Greece	1	11.2	0.09
Romania	1	21.5	0.05
TOTAL	**1007**	**504.3**	**2.00**

ALTAVILLA A. et al. Acta Paediatrica 2012, vol.101, n.1, p.27-32

Independent ethical review

Role of ECs in paediatric research ?

- ECs lack of knowledge/awareness of the European regulatory framework and ethical issues related to paediatric research
- ECs lack of involvement in paediatric research in Europe

- ✓ **ECs could be able to provide opinions in the stringent and compulsory timelines?**
- ✓ **Is there a risk that tacit approval become "the way" of CT approval especially for complex paediatric trials?**

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Independent ethical review

Role of ECs in paediatric research ?

- to favour the **growing of competence** (e.g. awareness of scientific, methodology/ethical issues)
- to favour initiatives (e.g. debates, educational programme, training...) aiming at **harmonising practices**
- to develop **NETWORKING** among ECs and stakeholders

Enpr-EMA
European network of paediatric research at the European Medicines Agency

eurec

Enpr-EMA and EUREC and will explore ways of collaboration

✓ **to discuss those emerging issues and**

✓ **promote the dialogue between ECs and paediatric research**

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Independent ethical review

PDCO/Ethics Committees interaction ?

The opinions of the Paediatric Committee (PDCO) shall be taken into account in the assessment of anticipated therapeutic and public health benefits (art.6 CT Regulation)

- What could happen if PDCO approves the PIP but the RMS and/or the EC does not agree on the protocol of the same trial?
- Whose decision should prevail over the other?

- PDCO's decision only concern the PIP and not the protocol

- PDCO has a paediatric expertise that ECs and national authorities responsible of the protocols evaluation do not necessarily have

Further clarification would be helpful regarding interaction among PDCO/RSMS/ECs

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The new EU Regulation on CTs

The assessment of the benefit

DISTINCTION BETWEEN TRIALS
WITH

DIRECT BENEFIT FOR THE MINOR

outweighing the risks and burdens involved

SOME BENEFIT FOR THE POPULATION REPRESENTED BY THE MINOR

the participating minors cannot expect a personal health benefit whereas they face research risks/burdens

CT pose only minimal risk & minimal burden

in comparison with the standard treatment of the minor's condition

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The new EU Regulation on CTs

New European Ethical recommendations

Minimal risk/minimal burden criteria

CT will pose only MINIMAL RISK to & impose MINIMAL BURDEN on children

in comparison with the standard treatment of the minor's condition

- **Risk** : as the probability and magnitude of harm anticipated in the CT assessed also in terms of duration and repetition
- **Burden** : as the (mostly) subjective load that affects a participant, parents and family (pain, discomfort, fear, disturbances of lives and personal activities)

Both risks and burden may be physical, psychological, or social, may be immediate or delayed, and may vary according to age, duration, previous experience, repetition or accumulation

Risks and burden should be continuously monitored,
Stopping rules should be included under the DSMB supervision with paediatric experts as pre-specified in the protocol

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Minimal risk and minimal burden prerequisite for paediatric research

ETHICAL GUIDELINES

Except for the ICH-GCP :

- ✓ *Declaration of Helsinki*
- ✓ *CIOMS* guidelines
- ✓ *UNESCO Declaration on Bioethics and Human Rights*
- ✓ *EU Ethical Recommendations 2008*

LEGAL INSTRUMENTS

EUROPEAN/INTERNATIONAL

- ✓ *COE Oviedo Convention and its Additional Protocol on Biomedical Research*

NATIONAL LAWS

- ✓ *Austrian / Danish /French / German/ Dutch / Spanish law*
- ✓ *US and Canada law*

Most of these texts do not define what constitutes minimal risk
When definitions are provided, there is a lack of consistency among them

Gennet E., **ALTAVILLA A.,** ***"Paediatric research under the new EU regulation on clinical trials: old issues new challenges",*** EJHL, 2016, Vol. 23, n.4: 325 – 349

Minimal risk /Minimal burden definitions

A **risk** is considered ***minimal***

"if the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests" (45CFR 46.102)

Absolute interpretation

- could hinder valuable research by limiting acceptable risk to very low
- Could not be protective enough in some cases (child living in socially, geographically dangerous areas)

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

The research bears a **minimal risk** if, having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned.

Relative interpretation

- Linked to the health of the child thus adressed on a case-by-case basis
- Permits to conduct research with higher risks in sick children (weaker protection for more vulnerable children)

Ambiguities remain and a lack of consensus

Gennet E., **ALTAVILLA A.,** ***"Paediatric research under the new EU regulation on clinical trials: old issues new challenges",*** EJHL, 2016, Vol. 23, n.4: 325 – 349

The new EU Regulation on CTs

New European Ethical recommendations

Minimal risk/minimal burden assessment

RISK and BURDEN have to be assessed as MINIMAL

in comparison with the standard treatment of the **minor's condition**

Minimal risk can be defined as the probability and magnitude of harm or discomfort similar

- to risks ordinarily encountered in a child's daily life, or
- during the performance of routine physical or psychological examinations, or simple tests in a child

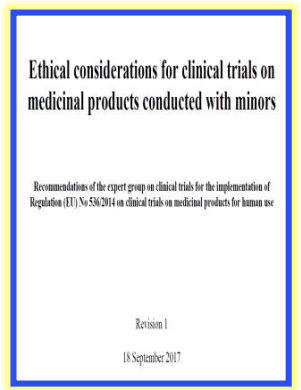
Minimal risk and burden viewed in the context of the disease, health status, prior experiences and standard treatments of the participants

Minimal risk/minimal burden assessment in population benefit CT

Standard treatment

Treatments used as comparators should be evidence based

Since in paediatric medicine the level of evidence may be poor, **best practices or usual healthcare would qualify as standard treatment**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If there are **multiple standard treatments**

- each should be described in the protocol
- respective risks and burdens assessed

standard treatments can change
depending on the condition/the phase of the disease
risk and burden can differ substantially
Careful ethical review is required to guarantee the best interest of the child

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Minimal risk/minimal burden assessment in low-intervention CT

Normal clinical practice (NCP)

The treatment regime **typically followed**

to treat, prevent, or diagnose a disease or a disorder

No further clarifications in the updated EC Ethical recommendations

- What is the exact difference between 'standard treatment' and (NCP)?
- NCP could be defined as 'routine examination'? As" usual care"?
- Could standard treatment entail higher risks than NCP?
- Should we consider NCP the treatment tipically followed for a healthy or sick child?
- Does 'normal' mean the statistically most frequent practice or the latest available treatment ? In all the countries ?
- If so, how are NA/ECs going to gather empirical data on each type of practice?

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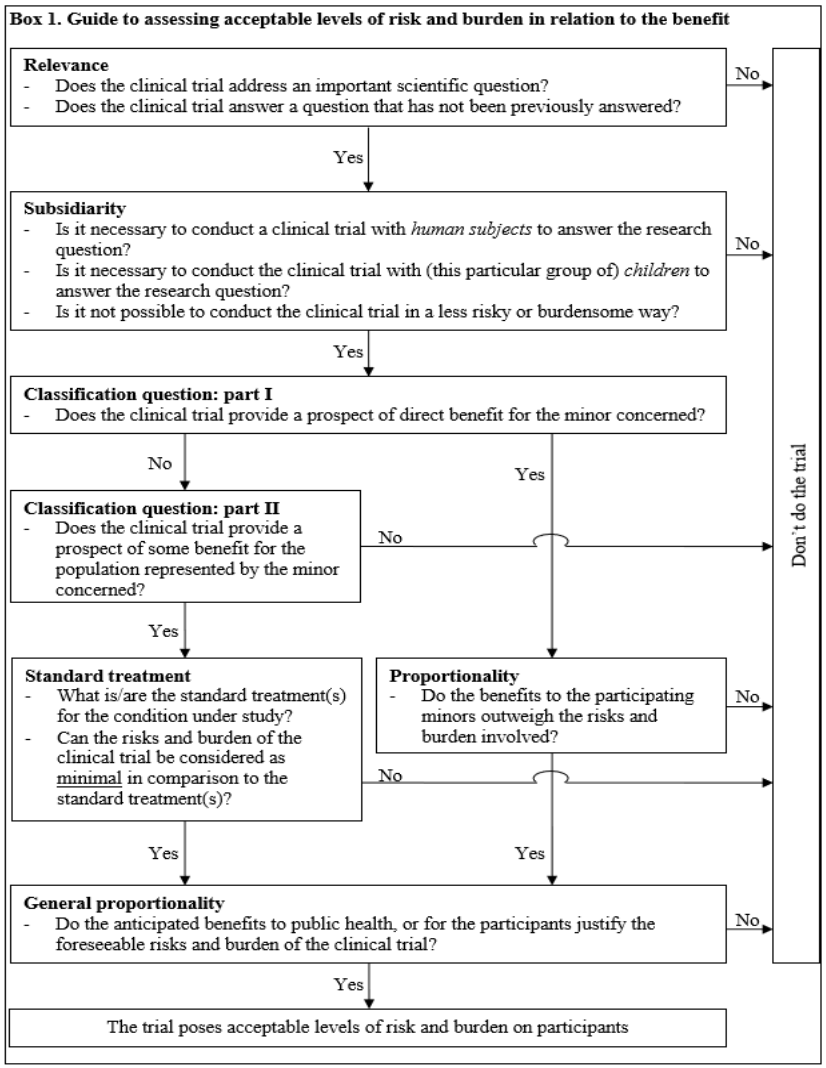
New European Ethical recommendations
Risk/benefit assessment

Box 1: Guide to assessing acceptable levels of risk and burden in relation to the benefit



ANNEX 3: Examples for levels of risks and burden of study procedures

Procedure	Description of the elements of risk and burden to be evaluated
Allergen challenge / hyper reactivity test	Skin tests involve, for a variable and individualised number of antigens, to scratch a subject's skin with a sharp instrument (prick test) or to inject a small amount of fluid into the skin (intradermal test), or to place a patch (epicutaneous or patch test) often in an inaccessible place (e.g. back). An airways hyper reactivity (bronchial provocation or bronchial challenge) test involves the controlled inhalation of agents that can temporarily induce wheezing and reduce lung maximum forced expiratory flow rates. Risks include erythema, swelling and itching that could persist for hours and respond little to treatment; the need for medication after bronchial provocation testing, as well as a rare anaphylactic shock. Burdens may include fear and discomfort experienced with the skin reactions, respiratory distress, the duration of the procedure and the need of staying in a health professional setting.
Anaesthesia (local, regional, general)	A range of agents and techniques are used for anaesthesia. Local, regional and general anaesthesia can be distinguished and generally represent an increasing level of risks and burdens. The level may also increase with deeper and longer anaesthesia. Risks include hypoxia, nausea and vomiting, cardiovascular, respiratory and neurological problems, and the need for specialist setting. Burdens include pain, fear, discomfort and need of staying in a health

Risk/benefit assessment in paediatrics CT?

- ✓ How to obtain a consistent classification of direct benefit CT within and between MS?
- ✓ How to evaluate minimal risk and burden for paediatric trials in countries that ratified COE treaty containing the « relative definition »?
- ✓ How clearly identify standard treatments in paediatrics in EU and outside?
- ✓ How clearly identify normal clinical practice in paediatrics in EU and non-EU countries?

The prospect of direct benefit should never be used to induce participation or raise false hope for families

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EU legal framework for paediatric research implies major important achievements

Despite the adoption of new specific rules, **many clarifications are still needed**

especially for

- The concepts of minimal risk/burden and standard treatment
- The concept of normal clinical practice in paediatrics for low-intervention trials
- Issues concerning the role and paediatric expertise of ECs and their interaction with the Paediatric Committee (PDCO)
- The conditions for processing paediatric data (especially in the case of secondary use of data in children) and
- The equivalence of CT regulation ethical standards for non-EU countries

Gennet E., **ALTAVILLA A.,** ***"Paediatric research under the new EU regulation on clinical trials: old issues new challenges",*** EJHL, 2016, Vol. 23, n.4: 325 – 349

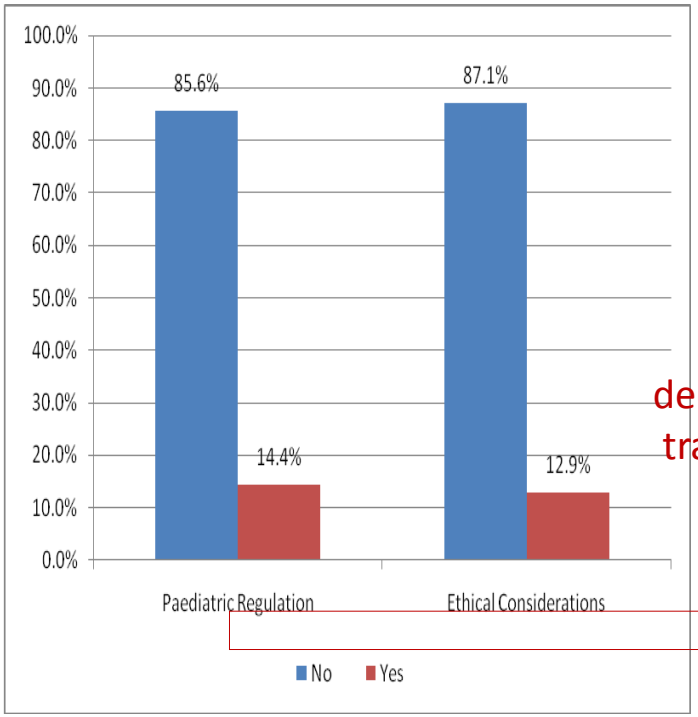
Giannuzzi V., **ALTAVILLA** A., et al., ***"Clinical Trial Application in Europe: What will change with the new regulation",*** Sci Eng Ethics. 2015 Jun 3, p. 1-16.

EU updated ethical recommendations for paediatric research

- provide recommendations on various ethical aspects related paediatric CT
- serve as a starting point, and stimulate reflection on the best interests of the children involved in trials

NO binding legal value

RESULTS : ECs awareness of the new regulatory framework



dedicated sessions or training initiatives

- 70% EU-15 (Belgium, Denmark, Germany, Italy, Norway, Portugal, Spain, Sweden)
- 30% new MS (Czech Republic, Latvia, Poland, Slovakia)

ALTAVILLA A. et al. Acta Paediatrica 2012, vol.101, n.1, p.27-32

To avoid that current discrepancies will lead to uncertainties in the assessment of paediatric protocols, especially in multicentre trials and trials in non-EU countries

To develop really "child centred clinical trials"

- Quality and accreditation system should be established for ECs
- Studies should be carried out regarding the risks and burdens really acceptable for children in different age groups
- Facilities should be appropriate to childcare to minimise pain, discomfort, and fear
- Personnel should be trained to look after and inform children/parents
- *Ad hoc* strategies to communicate with minors and legal representatives should be improved

Future challenges

Future pharmacopeia is more complex

moving away from allogeneic small molecules to

- ❑ complex autologous therapeutics (e.g. gene modified autologous immunotherapies)
- ❑ combinational strategies, utilising therapeutics and devices
- ❑ stratified and personalised medicine approaches
- ❑ tissue engineered approaches

Guidance and regulation must be continuously adapted and updated

Research, training and capacity building to address gaps in knowledge should be promoted

NEED OF STRONGER ENGAGEMENT AND

COLLABORATION AMONG ALL THE STAKEHOLDERS

(academia, industry, healthcare professionals, patients, media, regulatory authorities)

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