Protect the experimental patients population: a key role for Ethics Committees

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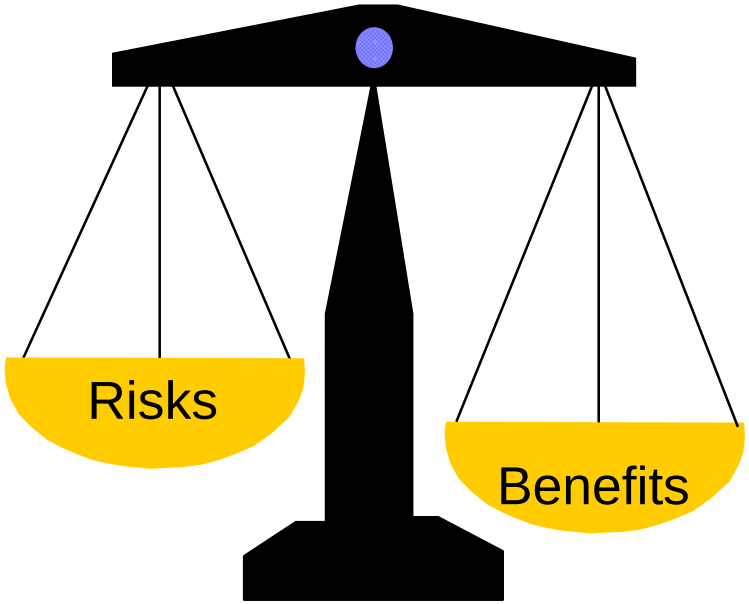
Disclamer

The views expressed during the presentation are the personal view of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the PDCO or/and the EMA.

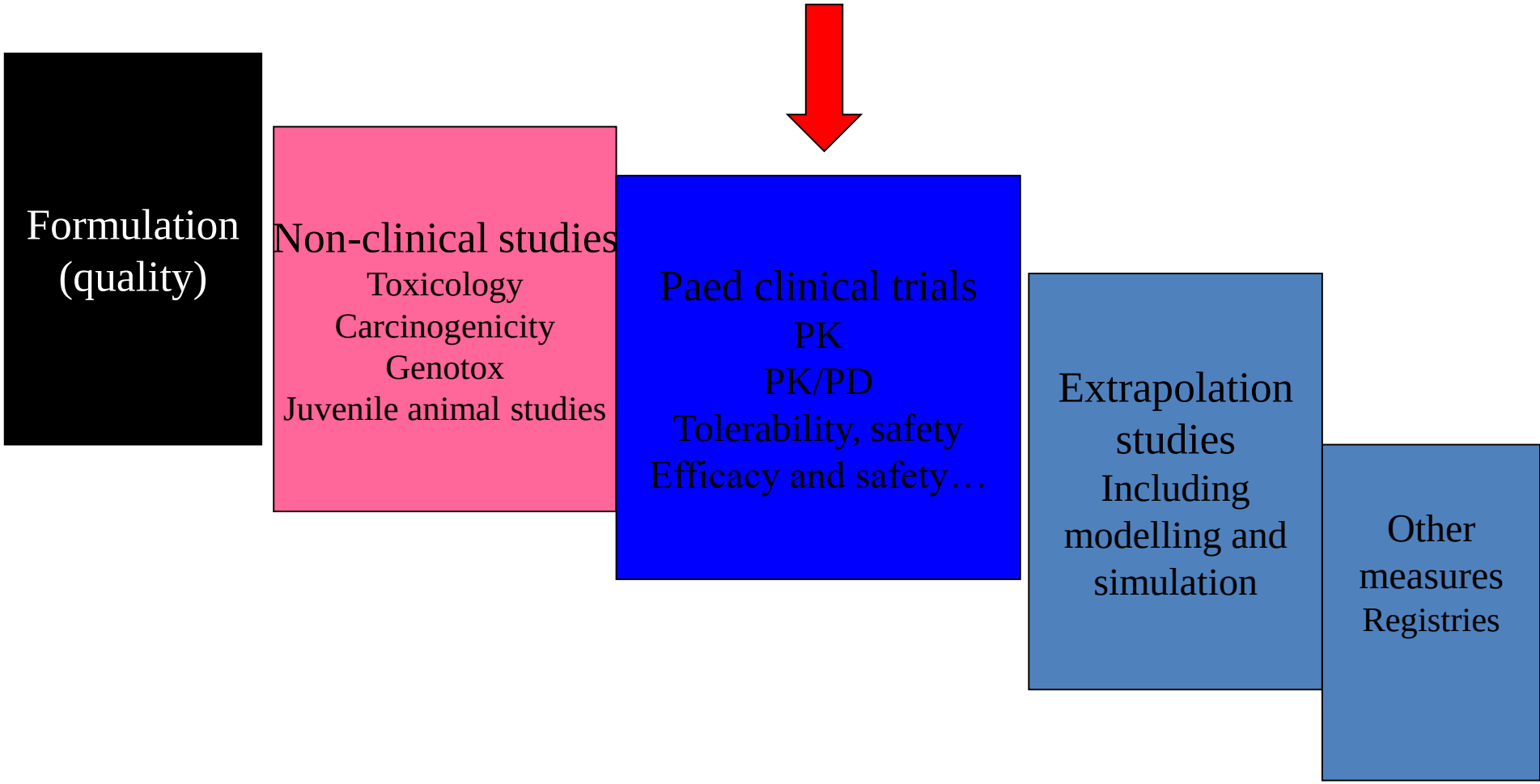
All presented data are publicly available.

CRITERIA FOR AUTHORISING MEDICINAL PRODUCTS



- The main scientific principle used in the evaluation of medicines is the **risk/benefit ratio** based on quality, safety, efficacy and risk management considerations.

Drug development



Risk during drug development

nature

Scientists in the dark after French clinical trial proves fatal

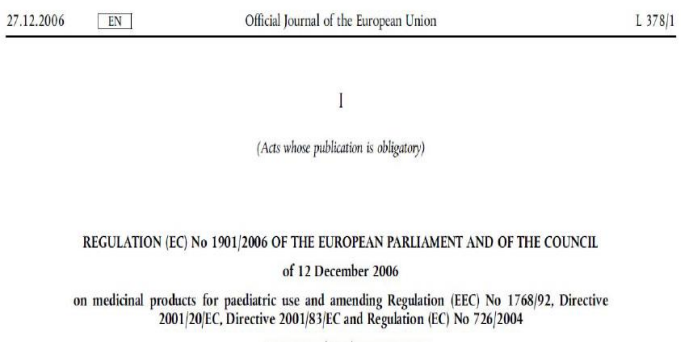
Knowledge about the drug's structure would help researchers understand what happened.

Declan Butler & **Ewen Callaway**

18 January 2016

One person died, and five others were hospitalized after a clinical trial of an experimental drug in France went tragically wrong ….

Objectives of the EU Paediatric Regulation



27.12.2006 EN Official Journal of the European Union L 378/1

I

(Acts whose publication is obligatory)

REGULATION (EC) No 1901/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

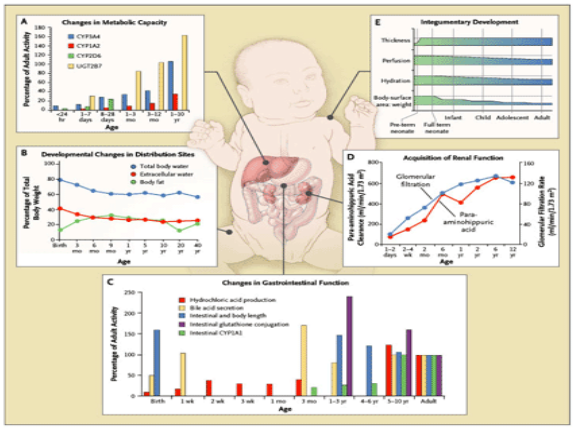
of 12 December 2006

on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

- Improve the health of children:
  - Increase high quality, ethical **research** into medicines for children
  - Increase **availability** of authorised medicines for children
  - Increase **information** on medicines
- Achieve the above:
  - Without unnecessary studies in children
  - Without delaying authorization for adults

Complexity of CTs in paediatrics

- changing medical knowledge
- changing medical needs
- developmental pharmacology
- pharmacogenomics
- pharmacovigilance
- changing legal framework



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

(Text with EEA relevance)

ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH MINORS

Recommendations of the ad hoc group for the development of implementing guidelines for Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

Concept 2016

ACTA PÆDIATRICA
NURTURING THE CHILD

Impact of the new european paediatric regulatory framework on ethics committees: overview and perspectives

A Altavilla[1], C Manfredi[2], P Baiardi[2], M Dehlinger-Kremer[3], P Galletti[4], A Alemany Pozuelo[5], J Chaplin[6], A Ceci (aceci@cvbf.net)[2]

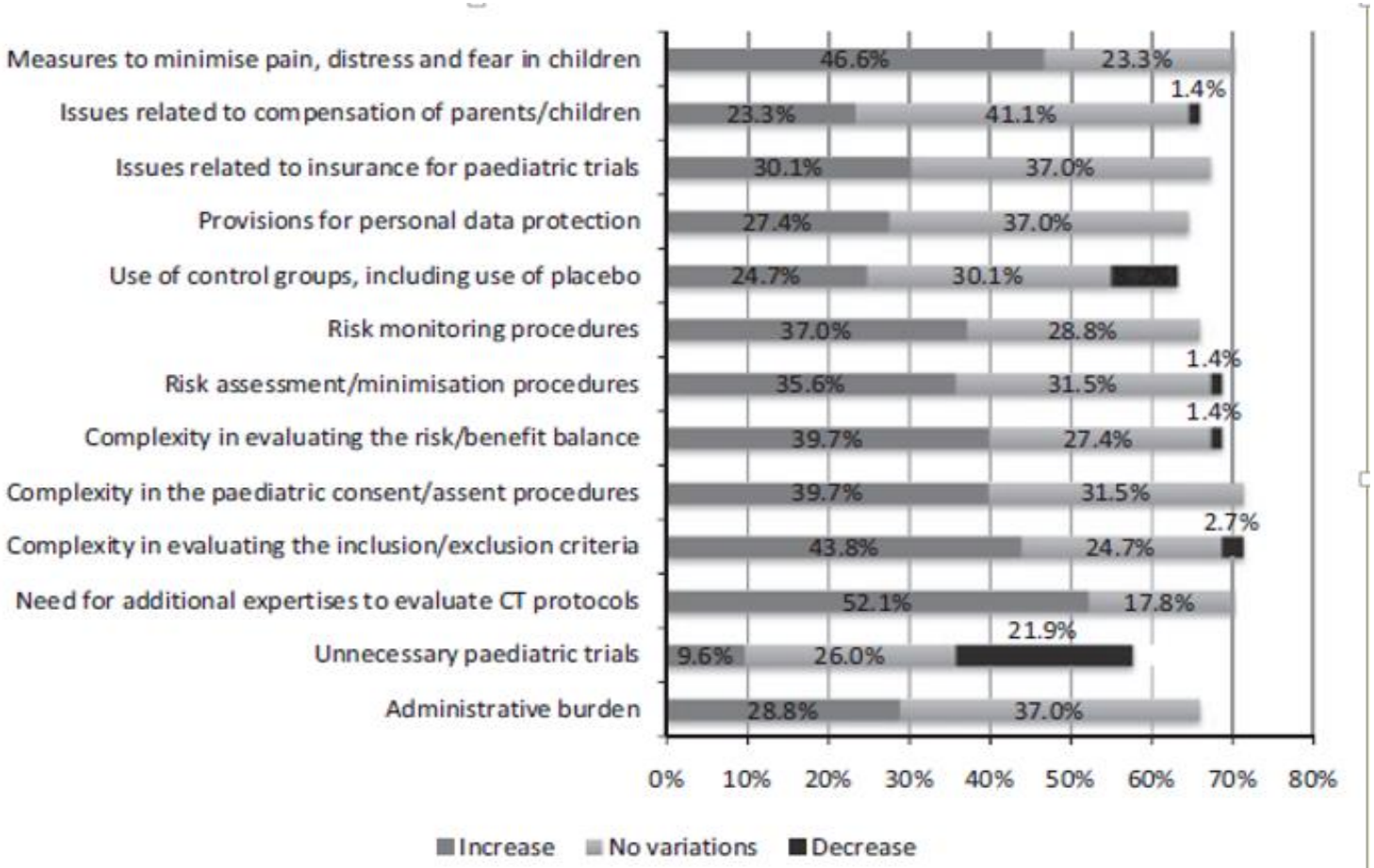


Figure 4 Main issues to be dealt with by Ethics Committees.

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Table 1 Ethics Committees existing in Europe

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

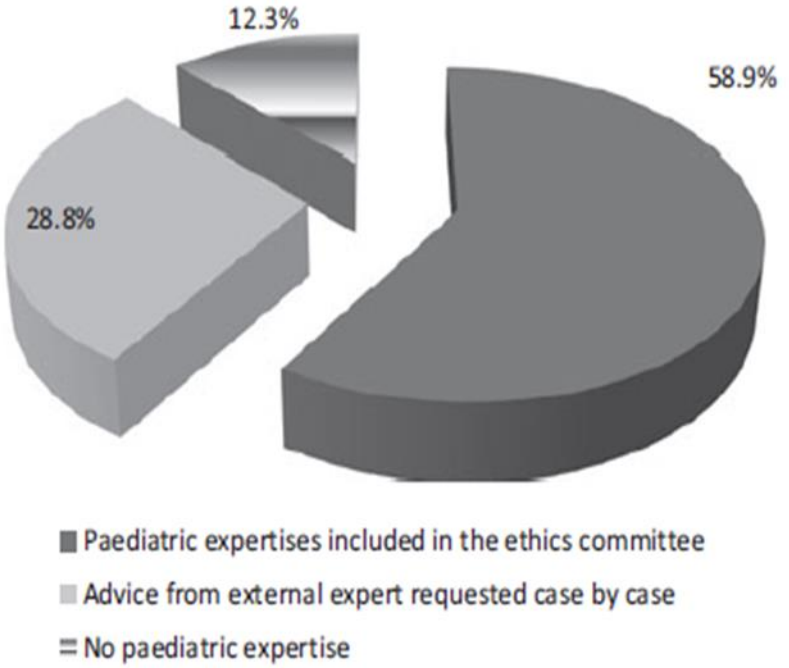

Figure 1 Paediatric expertise in Ethics Committees.

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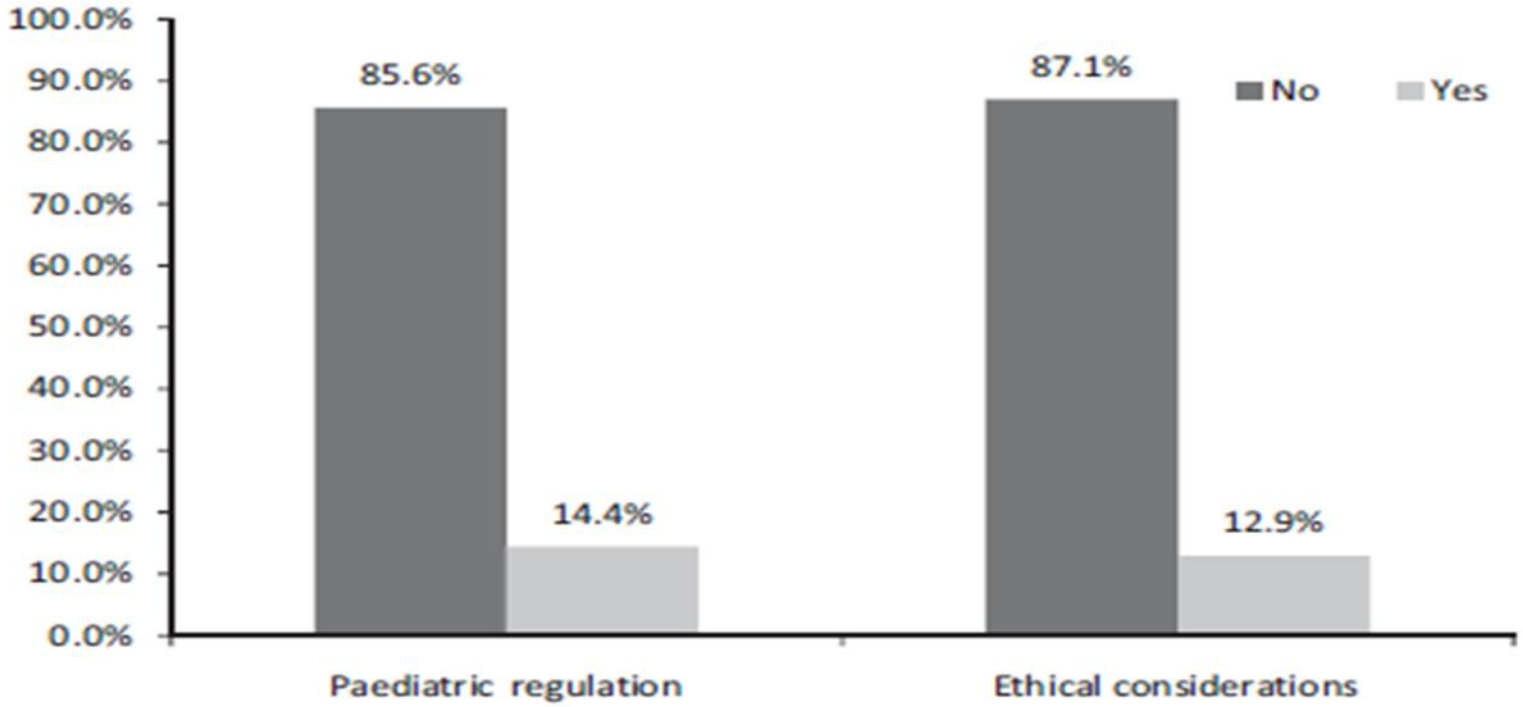


Figure 2 Ethics Committees formal knowledge of the current European paediatric framework.

Regulatory assessment of the PIP

Is there a paediatric need for a medicinal product which is planned to be developed?

What are currently drugs used for the indication?

Potential advantages of a proposed medicinal product over currently use drugs?

Differences between adult and paediatric patients?

Existing guidance on the condition /type of treatment (scientific or EMA/NCA guidelines, registries, formularies)

Regulatory assessment of the PIP

Is there a need to run clinical trials in paediatric population – which data are needed

PK?, safety? , efficacy/safety?

Design of studies (active comparators, placebo, placebo add on standard therapy, appropriate (validated) PEs and SEs, sample size (properly calculated), popPK

Advices received from any regulatory authority relevant to the development of the medicinal product for paediatric population

Regulatory assessment of the PIP

Are there enough paediatric patients to be included in the trials in the same therapeutic area?

Role of extrapolation, simulation?

How to minimalised potential risk/harm for children enrolled to CTs

Use of a DSMB

Need for long term follow-up of potential safety issues > what should be a period of observation

Ethical aspects - what is unknown at the time of PIP evaluation

Impact of changing enviroment (medical knowledge, new diagnosic/therapeutic oportunitis) within approved timelines (years !!!)

Exact information on investigators/ centres in terms of experise on specific paediatric problems

Full documentation of the CT (approved protocol, information for patients/parents and informed consent forms)

Placebo – regulatory perspective

London, 28 June 2001
EMEA/17424/01

EMEA/CPMP POSITION STATEMENT ON THE USE OF PLACEBO IN CLINICAL TRIALS WITH REGARD TO THE REVISED DECLARATION OF HELSINKI

states that *"in general clinical trials shall be done as 'controlled clinical trials' and if possible, randomised; any other design shall be justified. The control treatment of the trials will vary from case to case and also will depend on ethical considerations; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo".*

Council Directive 75/318/EEC also specifies that "*all clinical trials shall be carried out in accordance with the ethical principles laid down in the current revision of the Declaration of Helsinki*".

states[1] that *"The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not preclude the use of placebo, or no treatment in studies where no proven prophylactic, diagnostic or therapeutic method exists."* A strict interpretation of the Declaration appears to rule out clinical trials that use a placebo control arm whenever authorised therapeutic methods already exist, preferring active controls.

Placebo – regulatory perspective

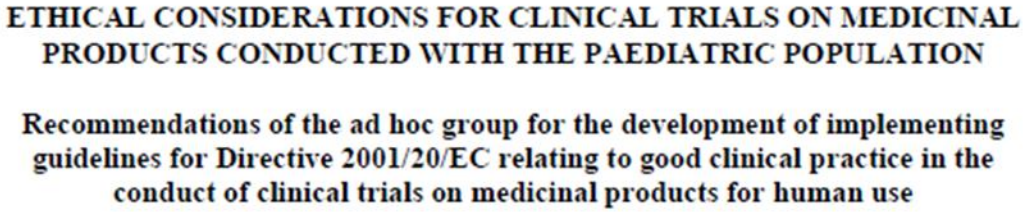
November 2010
EMA/759784/2010
Committee for Medicinal Products for Human Use

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available

Objectives of pivotal clinical trials are:
to demonstrate superiority to placebo
or
to demonstrate non-inferiority or equivalence to active control

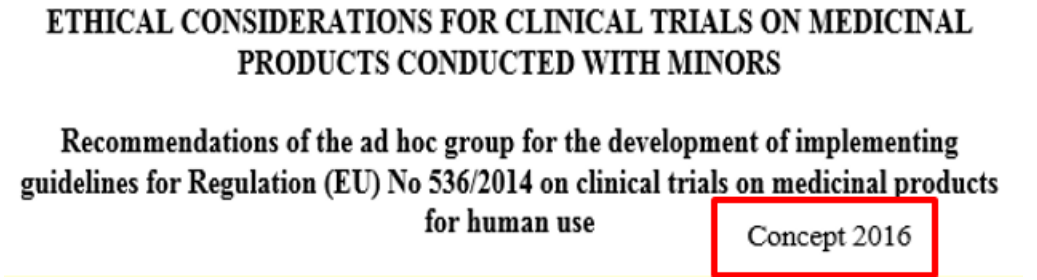
Placebo – ethical aspects


ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH THE PAEDIATRIC POPULATION

Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use

- placebo is not equivalent to absence of treatment, could be used on top of standard care (add-on)
- use of placebo may be warranted when evidence for any particular treatment is lacking or when placebo effect is known to be very variable
- placebo should not to be used when it means witholding effective treatment

Placebo – ethical aspects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Concept 2016

- use of control groups, including use of placebo should be based on equipoise, should be appriopriate to the condition investigating in the trial, and should be justified scientifically
- long-term use (beyond 3-6 months) is known to create difficulties in acceptance of the trial by participants and to increase drop-out rates

Placebo effects in children: a review

Katja Weimer, Marco D. Gulewitsch, Angelika A. Schlarb, Juliane Schwille-Kiuntke, Sibylle Klosterhalfen & Paul Enck

Affiliations | Corresponding author

Pediatric Research (2013) **74**, 96–102 | doi:10.1038/pr.2013.66

Pediatric RESEARCH

Placebo:

- > 155000 citations at PubMed
- only approx. 9000 related to children/adolescent
- approx. 2000 related to placebo effect per se
- only 50 discussed the placebo effect in children/adolescents

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Pediatric RESEARCH

Placebo effect is different in children vs adults

Table 1. Placebo response rates in children, adolescents, and adults with psychiatric disorders

	MDD (%)	OCD (%)	AD (%)	References
Children	60	40	42	29
Adolescents	49	32	32	29
Pooled	50	31	40	29
Adults	38	23	33	17,82,83

"Pooled" refers to the pooling of data for children and adolescents in ref. 29.

AD, anxiety disorders without OCD; MDD, major depression disorder; OCD, obsessive–compulsive disorder.

Informed consent for paediatric clinical trials in Europe

Pirkko Lepola,[1,2] Allison Needham,[3] Jo Mendum,[4] Peter Sallabank,[5] David Neubauer,[6] Saskia de Wildt[7]

Arch Dis Child. 2016 Nov; 101(11): 1017–1025.

	Consent/assent from child*		Consent from parent(s)/guardian(s)
Country	Legal age of consent†	Mandatory/suggested age ranges defined for assent (or consent if assent not used)‡	Number of required signatories
Austria	Not specified Practice—14 years	8–13 years EC may require younger assents	Both parents
Belgium	18 years	4–11 years (some sites do not use under 12 years) 12–14 years 14–17 years	One parent at recruitment, but both parents at some point for signatures
Bulgaria	18 years	6–11 years 12–14 years 14–17 years—use own consent+parental signature also required	Both parents
Croatia	Nothing specified	Nothing specified	Nothing specified

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Arch Dis Child. 2016 Nov; 101(11): 1017–1025.

	Consent/assent from child*		Consent from parent(s)/guardian(s)	General informed consent information	
Country	Legal age of consent†	Mandatory/suggested age ranges defined for assent (or consent if assent not used)‡	Number of required signatories	Official language requirements	Consent template(s)/guidelines/information sources
Italy	18 years	6–10 years 11–14 years 15–17 years—with own signature No official mandatory age(s) for assent. Different age-tailored assents are submitted voluntarily, and are evaluated by the ECs	Both parents	Italian	The Italian Medicines Agency http://www.agenziafarmaco.gov.it/en/content/clinical-trials the Italian regulation on CTs include the following: D.lgs 211/2003 http://www.agenziafarmaco.gov.it/sites/default/files/decreto_24062003_inglese.pdf DM 21/12/07 https://www.agenziafarmaco.gov.it/ricclin/sites/default/files/files_wysiwyg/files/Normativa/MD_21_December_2007_CTAform_English.pdf

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Arch Dis Child. 2016 Nov; 101(11): 1017–1025.

- The 'Informed Consent and Assent Tool Kit' is a publicly available resource for stakeholders involved in the running of paediatric clinical trials in Europe.
- These data provide a new platform for proactive feedback from stakeholders to maintain a common resource and approach to consent and assent requirements in Europe.
- These data hope to promote discussion for long-term decisions and practical changes leading to uniform ethics committee procedures across the European Economic Area.

Informed consent for paediatric clinical trials in Europe

Pirkko Lepola,[1,2] Allison Needham,[3] Jo Mendum,[4] Peter Sallabank,[5] David Neubauer,[6] Saskia de Wildt[7]

Arch Dis Child. 2016 Nov; 101(11): 1017–1025.

- There are noticeable differences between national consent and assent requirements for paediatric clinical trials in Europe due to national laws and regulations.
- The international and the ethics societies' guidelines are not based on uniform standards and rarely provide detailed consent or assent recommendations for children.
- A single source of comprehensive multinational data on informed consent and assent requirements of paediatric clinical trials across Europe is not publicly available.

New collaboration EUREC - Enpr-EMA

As of 2017, EUREC and Enpr-EMA (the European Network of Paediatric Research at the European Medicines Agency) are exploring ways of collaboration. As a first step, both will collect ideas for collaboration and collect a survey on needs and expectations among their members.

www.eurecnet.org

E-Learning Modules Log-in Required

a web-based learning program and certification

Module 1	**Introduction to Research Ethics** [EN] [FR] [DE] [PT] [PL] [PT-BR]
Module 2.1	**Research Ethics Evaluation** [EN] [FR] [DE] [PT] [PL] [PT-BR]
Module 3.1	**Informed Consent** [EN] [FR] [DE] [PT] [PL] [PT-BR]
Module 3.2	**Good Clinical Practice E6(R2) 2016** NEW! [EN] [FR] [DE] [PT] [PL]
Module 3.3	**HIV Vaccine Trials** [EN]
Module 3.4	**Adolescent involvement in HIV prevention trials** [EN]
Module 3.5	**Public Health Research Ethics** [EN] [FR] NEW!

Thank you for your attention. Awaiting for questions.....