07June2018

WORKING GROUP 4:

DIALOGUE AND INTERACTION WITH ETHICS COMMITTEES

Pirkko Lepola

EnprEMA WG 4 - Ethics

WG4 re-organization since 01Nov2017:

Primary members -> drafting documents

- Pirkko Lepola, Chair (Finnish Investigators Network for Pediatric Medicines, Helsinki, Finland)
- Maxine Kindred, (Janssen Research & Development, Buckinghamshire, UK)
- Viviana Giannuzzi (Fondazione per la Ricerca Farmacologica Gianni Benzi, Valenzano, Italy)
- Heidi Glosli (Oslo University Hospital, NorPedMed, Oslo, Norway)
- Martine Dehlinger-Kremer (SynteractHCR Deutschland GmbH, Munich, Germany)
- Harris Dalrymple (PRA HealthSciences, Reading, UK
- Peter Sallabank (RegulinX, Surbiton, UK)
- David Neubauer (University Children's Hospital, Ljubljana, Slovenia)
- Geraldine Boylan (Irish Centre for Fetal & Neonatal Translational Research, University College Cork, Ireland)
- Jean Conway (Irish Centre for Fetal & Neonatal Translational Research, Paediatric Unit, Cork University Hospital, Cork, Ireland)

Co-members -> reviewing documents

- Christina Manfredi (CVBF-Consorzio per Valutazioni Biologiche e Farmacologiche, Pavia, Italy)
- Jo Mendum (PRA HealthSciences, Reading, UK
- Diane Hoffman (prev. Janssen Research & Development, US – Retired !)

EnprEMA WG 4 - Ethics

Role:

Develop pragmatic responses to be implemented within six months (approx.!);

- **Examples of good practice when ECs consider trials relating to children and young people**
- **Develop proposals to disseminate examples of good practice to ECs**

Background I

Enpr-EMA WG 4 ethics list of deliverables – 2018

Year	Deliverable	Publication / Actions
2013	**Plan Report for Implementation** – Identification of problems & challenges and needed actions & proposed actions	• Recommendations (12), published in December 2013 for Enpr-EMA (only).
2015	**1. Deliverable**; "Tool Kit" - Informed Consent and Assent for Paediatric Clinical Trials in Europe	• Published on Enpr-EMA web-site on 18 December 2015; updated by the Enpr-EMA secretariat
2016	**1. Article**: "Informed Consent for Paediatric Clinical Trials in Europe"; Authors: Pirkko Lepola, Allison Needham, Jo Mendum, Peter Sallabank, David Neubauer, Saskia de Wildt	• Published on 25 May 2016, Archives of Disease in Childhood
2016	**2. Deliverable**; Public Consultation of the "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population" (2008), open June-August 2016 Contributed by EFGCP CMWP (European Forum for Good Clinical Practice, Children's Medicines Working Party; WP 1, In collaborating with a small group of EMA PDCO members, submitted 30 August 2016.	• Revision 1 of the document published on 18 September 2017 on EudraLex Vol.10. Clinical Trial Guidelines, Chapter V - Additional information

Background II

2016	I. **Contribution to PROPOSED CHANGES TO THE U.S. COMMON RULE** Implications for Pediatric Research (Federal Policy for the Protection of Human Subjects) Included comments on two points relating to paediatric research: 1) the value of taking an international perspective when revising the Common Rule 2) Informed Consent. Comments submitted on January 2016 by Mark Turner, the behalf of the Enpr-EMA	• The revised Common Rule becomes effective on January 19, 2018 in US
	II. **Collaboration with the European Network of Research Ethics Committees (EUREC)**- Enpr-EMA started	• EUREC presentation in Enpr-EMA Annual WS, May 2016 • 1st Enpr-EMA WG4 presentation in EUREC meeting, 08Sep2016, Helsinki
2017	**3. Deliverable**: "Harmonized General Informed Consent / Assent template – document for European Paediatric CTs" Based on: ➢ identification of all similar elements across assents / consents of publicly existing templates	• 1. version published on Enpr-EMA Annual Workshop, 16 May 2017, IC/Assent template model – Version 3.0 (2017) • *For all stakeholders: to be placed publicly available on Enpr-EMA web-site, plan; -> by 06/ 2018*

Background III

	➢ Comparison of the review responses with the EU Ethics Guideline (Revision 1); published in October 2017 ➢ Identification of any conflicting elements across template ➢ Correcting the template according to EU CTR ➢ Include all important elements from eYPAGnet Reports ➢ Including EAP Ethics WG comments	• *Publication in 2018 ?*
2017	III. **Collaboration European Network of Research Ethics Committees (EUREC)- Enpr-EMA Cont.;** • Enpr-EMA WG4 presentation in EUREC-ANCEI Congress in Barcelona,18May2017 • Discussion, "brainstorming" TC, 03Oct2017 • 1st Meeting in London 13th November 2017, EMA	• 4 Action points agreed; 1) Map currently available "ethics" -training programmes for investigators – both e-based and f-2-f 2) Compile available guidance documents (e.g. GRIP placemat, Ethical considerations for clinical trials in minors, etc.) and prepare a template / material package, including involvement of PPGs/YPAGs for PDCO 3) Share UK experience with documentation of patient/young people involvement 4) Ensure inclusion of paediatric research aspects in EUREC training boot camp planned in April 2018 in Helsinki

Enpr-EMA WG4 – Task 3

3rd Task: Original Plan: Partly harmonized core IC / Assent template with standard language (English) 2016-2017

Based on the following background facts:

1. New EU CT Reg. (impl.approx.10/2018) will harmonise the clinical trial application (CTA) process, but IC/Assent issues remain with each Member State.

2. There are noticeable differences between national IC and assent requirements in Europe due to national laws and regulations (See: Tool Kit data)

3. These discrepancies can present challenges for multicentre paediatric CTs

3. Deliverable: Original Plan"Partly harmonized of Informed Consent / Assent template -document"

- Based on identification of all similar elements across assents / consents of existing templates

Enpr-EMA WG4 – Task 3

3. Task – Part I -: Executed by a "Mini-Group of Consents"

- **Diane Hoffman :** Johnson & Johnson Pediatric Center of Excellence (Chair)
- **Maxine Kindred :** Johnson & Johnson Operations (Operational producer)
- **Heidi Glosi :** Oslo University Hospital (support)
- **Jo Mendum :** CRO, PRA (support)

3.Deliverable – Part I -: Comparison of Assents from WHO, MCRN and Finland

- Identification of all similar elements across assents
- Prepared to include all elements
- Items included in the WHO template was added to the guidance as they were deemed important to the assent

- Guidance template provided January 2017
- Presented in Enpr-EMA Annual Workshop **16May2017**
- Prepared the document for the Review process

Enpr-EMA WG4 – Task 3

eYPAGnet
European Young Persons' Advisory Group Network

FEEDBACK REPORT ABOUT:

ASSENT DOCUMENT TEMPLATE FROM ENPREMA WP ON ETHICS

PARTICIPANTS:

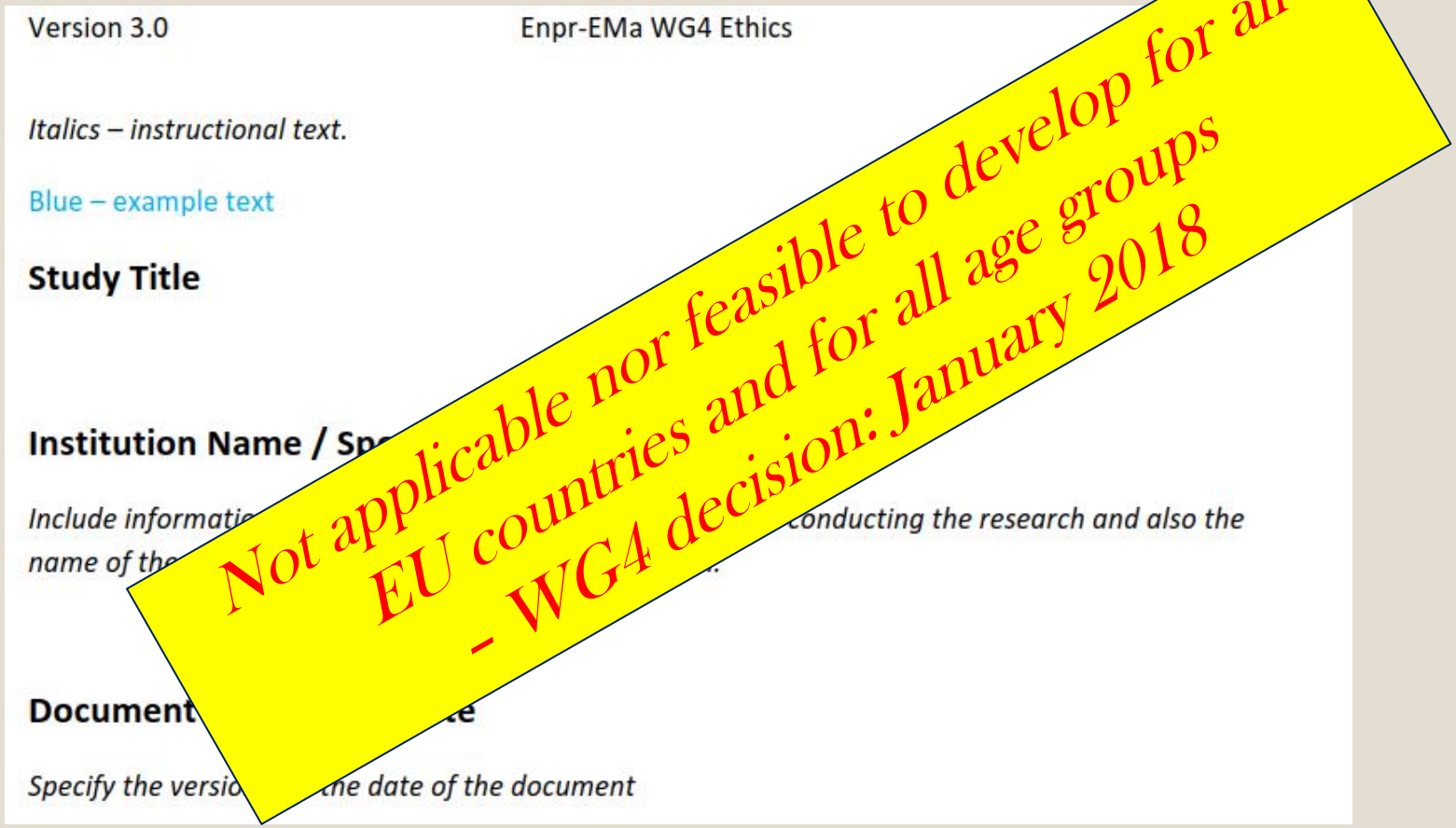
- Scottish Children's Research Network
- Generation R – Liverpool's team
- KIDS Barcelona – Sant Joan de Déu Children's Hospital
- KIDS France- Hospices Civils de Lyon

METHODOLOGY:

Monographic session leaded by the facilitator of every YPAG planned in June of 2017. The content of the session was:

- Introduction of EnprEMA and the role that plays regarding the paediatric clinical research along Europe.
- Explain the objectives of the Ethics Working Group of EnprEMA and the benefits to offer a standardized template of the assent document.
- Introduction of the assent template proposed, deep reading and discussion about the main features.
- Collection of individual feedback of all the attendees through a questionnaire that includes open questions (n=12) about: need of additional information, format, summary, etc.

Task 3. Assent / Consent – Model template - includes instructions



Enpr-EMA WG4 – Task 4

4. Task & Deliverable – Modified from the orginal Task 3 plan:

The Consent / Assent information as a Guidance Document for all Enpr-EMA stakeholders to be placed publicly available on Enpr-EMA web-site (-> by 06/ 2018) -> NO TEMPLATES

Process:

- Comparison of the review responses with the EU Ethics Guideline (Revision 1); published in October 2017.
- Correcting the guidance according to Ethics guideline (R1)and CTR
- Preparing to include all important elements from eYPAGnet Report
- Finalize the format

Review process of the Guidance Document

- **Drafting & Discussion (e-mails, TC) the format between;**

  April 2017 – April 2018 (Versions 1.0-3.0) including:

  - **European Academy of Pediatrics Feedback; 29June2017**
    > EAP Ethics Working Group Comments
  - **Inclusion of eYPAGnet Report Feedback; January 2018**
    > Children´s Voice
  - **Inclusion of revised EU Ethics Guideline (v.2.0); September 2017**
    > Ethical Proof
  - **Inclusion of legal EU documents: EU CTR (2014), EU GDPR (2018)**
    > Legal Proof

  + Language Proof (English)

The contents of the Guidance Document

- **Introduction + references** – 1 page
  - **3 figure-option´s menu for marking the need of inclusion of the information sections in Tables 1 and 2.**
- **Table 1: General Information requirements for Informed Consents & Assents (Agreements)** – 2 pages
- **Table 2: Trial Specific Information for Informed Consents & Assents (Agreements)** – 6 pages – 25 information sections
- Total of 9 pages.

Version 3.0 of the Guidance Document (p.1.)

WG4 Ethics **Assent / Informed Consent Guidance Document for Paediatric Clinical Trials in Europe** v.3.0 Draft 30May2018

This information template is a guidance document to support paediatric clinical trial conduct in Europe across all age groups; from birth to adulthood. As every country in the European Union and European Economic Area has national legislation and more detailed ethical requirements for Informed Consents and Assents for the conduct of paediatric clinical trials[1], and because these vary amongst the countries, this document may be used as a reference when preparing these documents according to the national regulations. The EU Clinical Trial Regulation No536/2014[2] (CTR, impl.2019) will harmonise the clinical trial application (CTA) process, but Informed Consent / Assent responsibilities remain with each Member State. The legal framework of this document describing the contents for patient information, and Informed Consents and Assents, is the current EU legislation[2] and EU Commission Ethical Guideline documents[3]. The additional practical examples are from the Ethics Working Groups of the European Network of Paediatric Research at European Medicines Agency (Enpr-EMA)[4] and the European Academy of Paediatrics[5]. Additionally, the eYPAGnet - European Young Persons´ Advisory Group Network[6], provided important feedback on the critical questions which need to be answered during the consent process. This guidance includes two tables; Table 1: General information and Table 2: Trial specific information.

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1 Lepola P., Needham A., Mendum J., Sallabank P., Neubauer D., de Wildt S. Informed Consent and Assent Tool Kit for Paediatric Clinical Trials in Europe. Arch Dis Child 2016;101:1017–1025.
2 European Union. 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. 16 June 2014
3 European Union Commission ad hoc Expert group. Ethical Considerations for Clinical Trials on Medicinal Products Conducted with Minors. Revision 1. 18 September 2017. Eudralex 10, Chapter IV-Additional Information.
4 European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). Available at: http://www.ema.europa.eu / Enpr-EMA Ethics Working Group
5 European Academy of Paediatrics, Working Goup of Ethics. Available at: http://eapaediatrics.eu/working-group/ethics/
6 eYPAGnet - European Young Persons´Advisory Group Network. Feedback Report from four national YPAGs to Enpr-EMA Ethics WG on Assent Document template, 25 November 2017.

Additional Task for eYPAGnet 05-2018

WG4 asked YPAGs feedback about

1) usefulness

2) functionality

Of the WORD READIBILITY SCORING function in order to pre-read the assent / consent / info-documents for better understanding (to avoid too complicate/non-understandable words).

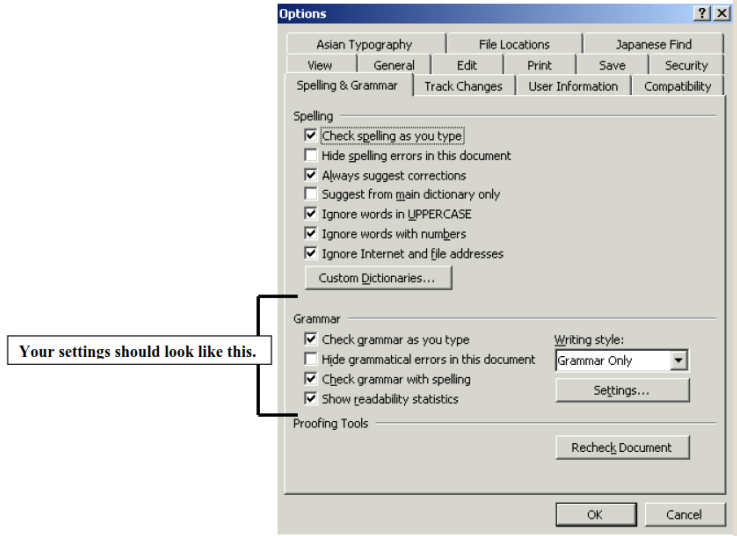
Our recommendation is avoid as much you can use this technology, because not has a EU background and never will be a 100% substitute of the feedback that children and young people can provide. If for any type of interest, for example the urgency to deliver a document, you will explore the use of these type of tools, our suggestion is to do study and compare the feedback that you can achieve from the tool and from the YPAGs.

Readability Scoring function in the English language version of MS Word. The Flesch-Kincaid method was devised in 1942; US centric tool.

How to assess the reading level of text using Microsoft Word

If you have a version of Microsoft Word for Windows, you can use it to determine the readability level of text. The following instructions are for Word 2000. Other versions should work in a very similar way.

First, click on "Tools" at the top of your screen. Then, click on "Options…" Toggle to the "Spelling and Grammar" tab. Your screen should look like the one below. Under the "Grammar" heading, make sure your settings are like these:



Your settings should look like this.

With the "Show readability statistics" option checked, you will get a report whenever you go through a spell check. To run a spell check, click on "Tools" and choose "Spelling and Grammar…" or, hit the F7 key.

Next steps

- **New eYPAGnet TASK:**
  - Design 3-pages long example assent / consent to proof it is possible (from complex and long document)
  - Needed for Guideline to work in practice: users must believe the requirements are reasonable and realistic
- Finalization of the Guidance Document with the whole WG4 (*acute new comments included*)
- Writing an article for a paper (*not yet decided*)

➢1. first placed to Enpr-EMA website

➢2. into the article with the copyright mark; © European Medicines Agency, 2018. Reproduced with permission.

Enpr-EMA WG4 + EUREC

New collaboration started with EUREC- European Network of Research Ethics Committees

- EUREC presentation in Enpr-EMA Annual WS, May 2016
- 1st Enpr-EMA WG4 presentation in EUREC meeting, 08Sep2016, Helsinki
- Enpr-EMA WG4 presentation in EUREC-ANCEI Congress in Barcelona,18May2017
- Discussion, "brainstorming" TC, 03Oct2017
- ***1st Meeting in London 13th November 2017, EMA***
- ***-> 4 Action Points for further activities***

THANK YOU!