Ethical issues and barriers for multi-national paediatric clinical trials: the challenging experience of the DEEP project

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The procedures and requirements to set up and submit clinical trials to Ethics Committees and/or Competent Authorities are not fully harmonised in Europe, and this is even more evident when non-EU Countries are involved (Giannuzzi V. et al, *in press*). This lack of harmonisation makes more difficult the approach in the case of 'small populations', such as children and patients affected by rare diseases, which typically are multi-centre and multi-national.
We are carrying out an efficacy-safety randomised, open label, non-inferiority active-controlled trial (DEEP-2) involving paediatric patients affected by transfusion dependent haemoglobinopathies from seven European and non-European countries (Albania, Cyprus, Greece, Italy, United Kingdom, Egypt, Morocco, Tunisia). DEEP-2 is part of a PIP (P/0331/2014) and performed in the context of the FP7 project (*DEferiprone Evaluation in Paediatrics*; FP7 HEALTH-F4-2010-261483).
In order to face diversities and divergences dealing with the trial population (i.e. a multi-ethnic population of children affected by rare diseases, recruited in countries with different cultures and laws), we followed a specific approach to submit and perform a GCP-compliant study and to guarantee high-level ethical standards in each trial site:

1. We overviewed the national procedures in each Countries participating in DEEP-2 in terms of authorisation procedures, timeframe for release of ethical approval, and protection of minor rights;
2. We implemented a unique procedure and a unique 'package of documents', having as reference the European legal framework;
3. We organised a 'trial management plan and infrastructure', including the preparation of specific Standard Operating Procedures (SOPs);
4. We developed a 'patients tailored approach', producing age-appropriate tools to increase the children empowerment in the assent process.

This approach resulted effective. By May 2015, the Clinical Trial Application has been performed in 19 out of 24 trial sites. 18 Ethics Committees granted the positive opinion, while the approval of the Cypriot one is still pending.
About 40% of the addressed Ethics Committees asked for changes and integration to the submission package. Ethical issues arisen during the approval process mainly dealt with contraceptive measures needed in the trial to prevent foetus damages, clarifications and additional information on the informed consent form.
Importantly, special authorisations were required besides the Ethics Committees' approval and the Competent Authorities' authorization: in Tunisia a special authorisation from the Ministry of Health was required for paediatric trials and in Egypt the approval from National Security was granted with the restriction for sample exportation.
In consideration of the above, the timeframes for the approval were delayed in the 60% of sites, thus being not compliant with the European requirements (60 days for single opinion release and 30 days for its acceptance).
In conclusion, the complexity related to 'clinical trials involving small populations' increases because of the multi-national nature of the trial, the involvement of children and the need to guarantee children protection.
The upcoming application of a stronger set of rules, issued by the new European Regulation on clinical trials, i.e. Reg. (EU) No 536/2014, is expected to harmonise practices, also outside Europe, as it states that clinical trials carried out outside the EU shall be conducted in accordance with the Regulation.

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Giannuzzi et al. Sci Eng Ethics. *In press*
European Parliament and of the Council of the European Union. 2014. Regulation (EU) No 536/2014. EU Official Journal, 2014,L158.