Ethics bureaucracy: a significant hurdle for collaborative follow-up of drug effectiveness in rare childhood diseases

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INTRODUCTION

Until a few years ago, a[1] majority of pharmaceutical drugs did not have any label for paediatric use; this situation prompted both the USA and European Union (EU) to pass specific legislation for clinical trials in children.[2–4] In Europe, extensive efforts have been made to facilitate drug development for children by setting up the Paediatric Committee at the European Medicines Agency (EMA), by implementing particular rules to enhance paediatric drug development, including orphan drugs which are often for children, and more recently by establishing the European Network of Paediatric Research at the EMA.[5–7] In the light of these efforts it is essential that other elements of the regulatory system work in the same direction and are not counterproductive. In a case study, we wish to highlight hurdles related to the ethical assessment that need to be addressed.

THE EUROFEVER PROJECT AND PRINTO NETWORK: A CASE STUDY

Assessment of drug effectiveness requires collaborative data gathering by several clinical and academic centres. For rare diseases and for paediatric studies in particular, this network must be widespread comprising many centres on a global level. As a result of the Swedish EU Presidency Conference 'Assessing Drug Effectiveness' on 29 July 2009, an initiative was taken to define factors of success and problems encountered by European clinical projects and networks from a drug effectiveness perspective. One of these projects was the EUROFEVER registry, aimed at collecting information on the clinical presentation, outcome and response to treatment of patients affected by autoinflammatory diseases in childhood.[4 8]

Autoinflammatory diseases are a group of rare conditions secondary to mutations in genes coding for proteins that play a pivotal role in the regulation of the inflammatory response. Among these, cryopyrin associated periodic syndromes are a group of conditions associated with mutations in the NLRP3, the gene coding for cryopyrin. Cryopyrin associated periodic syndromes are characterised by a chronic or recurrent systemic inflammation associated with a number of clinical features, such as urticaria-like rash, arthritis, sensorineural deafness, and central nervous system and bone involvement. The quality of life of these patients is severely affected.

The EUROFEVER registry gathers worldwide data on the natural history of these heterogeneous autoinflammatory diseases in order to identify different treatment strategies and their cost-effectiveness. The technical assistance for the implementation of the EUROFEVER registry (web database, data collection logistics), as well its use for participating centres, is provided by a worldwide non-profit network called the Paediatric Rheumatology International Trials Organization (PRINTO), which now includes centres from more than 50 countries worldwide.[4] The PRINTO network has been operative for several years performing phase II and III trials with biologic agents in juvenile idiopathic arthritis which eventually have been approved by regulatory authorities as well as other clinical studies regarding the more common paediatric rheumatic diseases.[9 10] Up to now PRINTO has gathered health information on more than 12 000 paediatric patients from over 40 countries.

Despite major improvements observed in the treatment of rare paediatric rheumatology disorders and the availability of a large network such as PRINTO a number of unsolved issues remain. These are listed below:

- the capacity of drugs to prevent the development of tissue damage after an early therapeutic intervention is unknown;
- blockade of specific cytokines raises a potential risk of serious side effects, especially in very young children with a long time span;
- for the majority of these rare conditions the use of biological and other standard treatment is still largely off label;
- patients' access to very expensive therapies vary geographically due to differences between national reimbursement schemes for drugs.

It is therefore necessary to carefully establish an assessment of expected long-term clinical benefits and the budgetary impact, that is, opportunity cost from a system perspective and fair access to treatment. The obvious way to answer these questions is to gather paediatric health information on a wide international base as set up by the EUROFEVER project and PRINTO.

HURDLES RELATED TO ETHICAL REVIEW

To highlight the burden of implementing paediatric studies we report the case of a clinical trial conducted by PRINTO in the rare disease juvenile dermatomyositis with off label drugs used in current clinical practice worldwide. It is of note that this is a purely academic trial managed by PRINTO, financed in part by the Italian Agency of Drug Evaluation (AIFA) and with no support from pharmaceutical companies. In order to collect data for this particular study comprising 130 patients from 30 different countries, participation of 103 clinical centres was needed. The PRINTO network has an efficient process for collecting data that meets regulatory demands. The major problem consists of bureaucratic constraints related to ethics approval. In this particular study, the process of obtaining

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ethical approval from the relevant ethical review boards took 2 years. The EU Directive for the ethical implementation of clinical trials gives latitude for national applications and adaptation to local organisational cultures. Accordingly, the Directive has been implemented in 27 different ways across Europe. In some countries, approval from one of the participating centres is sufficient, for example, France and Norway. In other countries, approval is needed from each regional or local ethical review board where the centre is situated, for example, Italy and Germany. In all, 97% of the ethical review boards gave their approval without requesting any change at all. There were three negative decisions, mainly related to the fact that the drug under study was not approved for use in children.

Another example is the non-interventional EUROFEVER registry study for which ethical committee approval for entering patients into the registry was obtained in the participating centres according to the laws in each country.[4] Up to July 2011, 1880 patients from 66 centres in 30 countries had been included with 30 (45%) of them requiring ethics committee approval. This process also took about 2 years to be completed.

The time- and resource-consuming procedure for obtaining the necessary ethics approvals in these multicentre and multinational collaborations is problematic from a moral, logistic and economic point of view. There is an opportunity cost both to the researchers and to society if time and money are spent on this ethical review process instead of being used for other purposes, for example, collecting and analysing data. There are other recent reports on the actual high costs, time delays and unmet patient interests associated with seeking advice from ethical review boards and similar advisory groups.[11–13] It has even been argued that time delays through the ethical review system cost lives.[14] One may at least question whether the ethical review system is doing its job, that is, keeping the central focus on what is best for the patient.[15] Taking all these points into account, we suggest that a real harmonisation is needed, moving from an EU directive to an EU legislation, where one approval from each country is sufficient, arguably through legislation and not just with the help of directives that can be interpreted differently in different countries.

As the vast majority (97%) of the ethics applications in the juvenile dermatomyositis study and the EUROFEVER registry study passed through the different national review systems without giving rise to any discussion that needed a comment or a request for revision, an alternative, simpler procedure is required. This procedure would regulate in more detail what kind of information should be given to the patients in association with registry research in clinical networks. That this information is included in the patient information could easily and simply be checked by a civil servant at the national regulatory authority, thus circumventing the seemingly unnecessary and costly ethical review process in all participating centres of an international paediatric initiative. We suggest the question-based template in box 1 as a provisional start.

Box 1 Heuristic template for patient information in association with clinical registry research

1. What is the purpose of the collection of data?
2. Will personal data be linked to other registries?
3. Will genetic information be used?
4. Who is responsible for the safety of data?
5. What is the identity of the data controller?
6. Will the research involve children/minors and is there a model for seeking their assent when minors and consent when they reach legal age?
7. Will the data be shared with international partners?
8. Are the data coded in accordance with EMA recommendations adopted by ICH (International Conference on Harmonisation of Technical Requirements) 2007 and CHMP (The Committee for Human Medical Products of the European Union) 2008 (identified, simple code, double code, anonymised)?
9. Will the collaboration include both academic and commercial partners?
10. Is the information only accessible by authorised persons?
11. Is individual data traceable and may it be withdrawn or anonymised?
12. Will the research, if successful, lead to inventions that will be patented?
13. Will individual and/or general results be returned to the patients?
14. Is the text of the consent/assent clear and concise to be understood by a family with different levels of education and by children with age adequate to provide assent?

CONCLUSION

The ethics review process has been put in place to protect patients and other research subjects against possible harm associated with biomedical research. As such, it plays an important role. However, if there is evidence that in certain instances the system, in itself, produces more harm than good, it should be modified. The bureaucratic problems encountered by the EUROFEVER registry and the PRINTO network indicate the need for such a change because from the perspective of the patient it is clear that spending 2 years on getting approval for uncontroversial research, which 97% of the ethics committees authorised without requiring any further information, is a waste of valuable resources. Clinical networks depend on voluntary work by devoted clinicians and have limited funding resources. Their time and resources should not be wasted on an unnecessarily bureaucratic ethics system.

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REFERENCES

1. **Ruperto N**, Martini A. Use of unlabelled and off licence drugs in children. A European paediatric rule is needed to protect children. *BMJ* 2000;**320**:1210–11.
2. **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. *Official Journal of the European Union.* 2006;L**378**:1–19.
3. Food and Drug Administration (FDA). Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biologic products in pediatrics patients (21 CFR Parts 201, 312, 314, and 601). *Fed Regist* 1998;**63**.
4. **Ruperto N**, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). *Arch Dis Child* 2011;**96**:596–601.
5. European network of paediatric research (Enpr-EMA). Recognition criteria for self assessment. 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/01/WC500100443.pdf (accessed 25 Jan 2012).
6. **Report** on second workshop of the European Paediatric Research Network (Enpr-EMA), 16 March 2010. http://www.ema.europa.eu/ema/index jsp?curl=pages/news_and_events/events/2010/02/event_detail_000173 jsp&murl=menus/news_and_events/news_and_events jsp&mid=WC0b01ac058004d5c3 2010:1–8 (accessed 25 January 2012).
7. **Ruperto N**, Eichler I, Herold R, *et al.* A European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA). *Arch Dis Child* Published Online First: 27 November 2011 doi:10.1136/archdischild-2011-300286.
8. **Ozen S**, Frenkel J, Ruperto N, *et al.*; Eurofever Project. The Eurofever Project: towards better care for autoinflammatory diseases. *Eur J Pediatr* 2011;**170**:445–52.
9. **Ruperto N**, Lovell DJ, Quartier P, *et al.*; Paediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008;**372**:383–91.
10. **Lovell DJ**, Ruperto N, Goodman S, *et al.*; Pediatric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;**359**:810–20.
11. **Metcalfe C**, Martin RM, Noble S, *et al.* Low risk research using routinely collected identifiable health information without informed consent: encounters with the Patient Information Advisory Group. *J Med Ethics* 2008;**34**:37–40.
12. **Noble S**, Donovan J, Turner E, *et al.* Feasibility and cost of obtaining informed consent for essential review of medical records in large-scale health services research. *J Health Serv Res Policy* 2009;**14**:77–81.
13. **Hansson MG**. Do we need a wider view of autonomy in epidemiological research? *BMJ* 2010;340:c.2335,1172-1174.
14. **Whitney SN**, Schneider CE. Viewpoint: a method to estimate the cost in lives of ethics board review of biomedical research. *J Intern Med* 2011;**269**:396–402.
15. **Hansson MG**, Chadwick R. Is medical ethics doing its job? *J Intern Med* 2011;**269**:366–9.

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