MedCrave
Step into the World of Research
Journal of Lung, Pulmonary & Respiratory Research

Mini Review
Open Access
CrossMark

Integrating scientific review, ethical assessment and the patient perspective in clinical studies-two cases

Abstract

The new European Clinical Trial Regulation536/2014 replaces the 2001 directive. Despite debates it remains a two-tier procedure and does not guarantee patient involvement. Using our experience in two European clinical projects, we provide support and recommendations to improve the new ethics assessment and monitoring procedure. The findings presented show that an integrated European-wide, multidisciplinary assessment from the ethical, safety, scientific and patients' perspective is achievable.

Keywords: ethics, clinical trials, patient involvement, european regulation

Volume 4 Issue 3 - 2017

Willem I de Boer,[1] Chris Gastmans,[2] Guy AM Widdershoven,[3] Damijan Erzen[4]

[1]Department of Pulmonology, Leiden University Medical Center, Netherlands
[2]Catholic University of Leuven, Belgium
[3]Department of Medical Humanities, VU University Medical Center, Netherlands
[4]Boehringer Ingelheim Pharma GmbH & Co KG, Germany

Correspondence: WI de Boer, Department of Pulmonology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, Netherlands, Email deboer.pim@hetnet.nl

Received: October 22, 2016 | **Published:** June 27, 2017

Introduction

The European Union (EU) Clinical Trials Directive 2001/20/EC regulated the administrative requirements and ethical and safety aspects of clinical trials on medicinal products for human use within the EU.[1] It was an assessment system with separate review procedures of clinical studies by national authorities on the one hand and a (medical) research ethics committee on the other. This double-review system is illogical, since performing research that is scientifically questionable is ethically not justified. The two-tier system is also time-consuming, bureaucratic, inefficient and increasingly expensive, as highlighted in reviews of the system and a survey by the European Commission (EC).[2-5] Moreover, the communication between the two review boards, their respective accountability and their capability of monitoring ethically approved studies is unclear and the role of the patient perspective is undervalued.

Integration of the ethical, scientific and patient perspective assessment seems better suited for most clinical studies.[6] A review from the patient's perspective is important as patients are affected by their own treatment and have the knowledge and experience of living with their disease every day. Having patients as partners in research ensures democratic decision making and the relevance of research, resulting in greater chances of societal implementation.[7-9] In 2014 the new clinical trial regulation was approved planning ethics review assessments for international clinical research at the European level and at the national level separately.[10] However, patient involvement is still not explicitly warranted. Here we discuss a best practice from two European multidisciplinary research consortia where the scientific and ethical review assessments were combined and the patient perspective was integrated.

Findings setting

The Innovative Medicines Initiative (IMI), a joint undertaking between the EC and the European Federation of Pharmaceutical Industries and Associations, provides grants for collaborative research projects. IMI aims to improve healthcare, treatment, patient-doctor-scientist-industry relationships and patient information. Healthcare and patient-representing organisations are involved as partners and stakeholders.[11] This paper focuses on IMI funded projects U-BIOPRED[12] and PRO active.[13] While both projects have medical objectives, U-BIOPRED had a strong life science focus towards an unbiased biomarker approach for severe asthma, whereas PRO active was looking at a clinically applicable, patient reported outcome measure capturing aspects of physical activity as experienced by patients. Both projects started in 2009 and ran initially for five years.

Within both projects, internal advisory boards dealt with ethical and patient safety issues from a patient, legal and scientific perspective (Table 1). The composition of the multidisciplinary boards is in line with European and national regulations, but include sup to 50% of patients from different European countries (Table 1). For patients, we developed membership criteria including higher education, interest in research, and ability to communicate in English with lay persons and scientists. This is in line with the proposed function and review role as described for professionals[6] and patients.[14,15] These boards reviewed and advised on study protocols, patient information sheets and informed consent forms (PIS-ICFs), and monitor all ethical, scientific conduct or safety issues arising during the study. For patient perspective issues, the boards were assisted by patient advisory boards (Patient Input Platform, PIP). The assessment was done simultaneously from a scientific, as well as an ethical and safety perspective and it specifically addressed the patient perspective. The U-BIOPRED safety monitoring board (SMB) had decisive capacities related to safety issues that can affect the study or project progress. In PRO active, safety monitoring was integrated in the ethics board (EB).

Table 1 Composition of the internal boards in two IMI projects

Project	Board Type	Discipline	Country
U-BIOPRED	Ethics Board	Biomedical Research	Netherlands
		Clinical Care	Germany
		Paediatric Care	United Kingdom
		Legal Affairs	Italy
		Research Ethics	Netherlands
		Patient	Lithuania
		Patient	United Kingdom
		Patient	United Kingdom
		Patient & Co-Chair	Netherlands
		Patient Represent & Chair	Netherlands
	Safety Monitoring Board	Clinical Care	United Kingdom
		Paediatric Care	Netherlands
		Clinical Pharmacology	Italy
		Biostatistics	Germany
		Patient Safety & Co-Chair	Germany
		Patient	Sweden
		Patient Represent & Chair	Netherlands
		Clinical Care	United Kingdom
		Biomedical Research*	United Kingdom
		Biostatistics**	Netherlands
		Patient Safety & Co-Chair	United Kingdom
PRO Active	Ethics Board	Legal Affairs	Germany
		Research Ethics	Belgium
		Patient	Netherlands
		Patient	United Kingdom
		Patient†	United Kingdom
		Patient***	Greece
		Patient Represent & Chair	Netherlands

†, Patient ceased in 2012; *, Scientist left board in 2011; **, Scientist joined board in 2010; ***, Patient left board in 2012

In both projects, English-language PIS-ICF templates were developed. These templates were adapted by the clinical research centres to the local situation. We developed novel instruments for healthcare and research professionals, so that they could participate in the advisory boards and perform their tasks. These instruments included monitoring criteria, appropriate ways for communication and discussion (e-mail, secured web forum, face-to-face meetings), charters and standard operating procedures.[16] The function of patients as lay persons was substantiated by the development of appraisal criteria that take different domains of the patient perspective into account.[8,17] The criteria included relevance for patients, improvement of quality of life, least burdening method for participants, compliance with regulations, clear lay and risk information to participants, and feedback of general results. One of the improvements was replacing the word "subject" in clinical studies with "person" or "participant". The profits of patient engagement in U-BIOPRED have been described previously.[18] We evaluated whether the boards contributed to the progress, quality and relevance of the projects. We studied the number of issues that the respective boards dealt with during the first 3.5 years, whether the advice was endorsed and implemented, and evaluated the process of interdisciplinary assessments and activities.

Content evaluation

We examined the number and type of responses given by the boards that were implemented into the protocols, PIS-ICF, and other procedures (Table 2). Types of responses were: a) a review in which documents were commented upon; b) advice on a question or issue arising from the project; or c) an action referring to a request by board members to partner organisations, for example handing over approval from local ethics committees. Table 2 shows the percentage of the responses that were endorsed or acted upon by the study leaders. In

U-BIOPRED, over 88% of the advice from the boards to the project partners was endorsed and implemented (EB: 22/25; SMB: 18/19). In PRO active, all advice was endorsed and implemented, resulting in adaptations of protocols and forms or texts.

Subsequently, we analysed the number and type of issues dealt with per advisory board (Table 3). Issues included: 1) recruitment rate; 2) lay language of the PIS-ICFs and brochures or web information texts; 3) methodological aspects in study protocols and PIS-ICFs (like safety and technical aspects of procedures, the need for nasal biopsies in U-BIOPRED, anonymisation procedure); 4) a better explanation of the study rationale, methods or rights of participants; and 5) feedback of results to participants. Differences between boards are related to ethical, safety or privacy issues regarding inclusion of participants (relatives, employees, patients already included in other studies), risk descriptions, such as radiation exposure and bronchoscopies or other methodologies, reporting of severe adverse events, and ensuring that the PIS-ICFs mention having an insurance for participants.

Table 2 Effectiveness of internal boards in two IMI projects

U-BIOPRED Type Response	Total Number	Implemented	%	PRO Active Type Response	Total Number	Implemented	%
EB				**EB-SMB**			
Review	8	7	87·5	Review	6	6	100
Advice	17	15	88·2	Advice	1	1	100
Action	0	0	0	Action	3	3	100
SMB							
Review	8	8	100				
Advice	11	10	90·9				
Action	0	0	0				

Table 2 shows the frequency of advice, reviews or actions that had to be taken by the different internal boards in the two IMI projects U-BIOPRED and PRO active.

Table 3 Frequency of discussion items of internal boards in two IMI projects

U-BIOPRED Ethics Board Items	Frequency	SMB Items	Frequency	PRO Active EB-SMB Items	Frequency
Recruitment	8	SAE Reporting	7	Methodology	7
Methodology	6	Risk Information	5	Lay Language	5
Feedback	5	Methodology	4	Explain	4
Ethics, Safety-Privacy	5	Explain	3	Ethics, Safety-Privacy	4
Lay Language	3	Insurance	3	SAE Reporting	3
Explain	3	Lay Language	2	Feedback	2
Risk Information	2	Recruitment	2	Confidentiality	2
Coi	2	Safety-Privacy	2	Insurance	2
Insurance	1	Feedback	1	Risk Information	2
Other	1	Confidentiality	0	Recruitment	1
Confidentiality	0	Involvement	0	Evaluation	1
SAE Reporting	0	Website	0	Other	1
Involvement	0	Evaluation	0	Involvement	0
Website	0	Coi	0	Website	0
Evaluation	0	Other	0	COI	0

Table 3 shows the frequency of items for which the respective boards requested adaptations in documents or experimental strategies by the researchers involved.
SAE, severe adverse event; COI, conflict of interest

Citation: Boer WID, Gastmans C, Widdershoven GAM, et al. Integrating scientific review, ethical assessment and the patient perspective in clinical studies-two cases. *J Lung Pulm Respir Res.* 2017;4(3):71–74. DOI: 10.15406/jlprr.2017.04.00126

Process evaluation

We also evaluated the process of interdisciplinary assessments and activities. All board members participated voluntarily. Upon a request for advice, the boards were informed within approximately two days. Reply time for the boards was set at 2-3 weeks. In U-BIOPRED the replies were given by 50.3%±22.3% (mean±SD) of the members in the boards with no differences between the boards. In PRO active 83%±13% of the EB members replied. All replies were given within the set time lines. Subsequently, the (co-) chair of the respective boards prepared a combined advice based on the replies within two working days. If needed, for example in case of further questions by board members, the advice was returned to the respective board. Where appropriate, the advice was adapted within one working day and sent to the study leaders. The total time for review or reply took 3-4 weeks. No differences in conduct or reply time were seen between the projects. The advice given contained elements related to ethics and/or patient safety, scientific and patient perspectives. Regular monitoring of the studies by the boards was based on newly developed criteria on ethics or safety aspects. This included safeguarding feedback of general results to study participants (done in year 4 of the studies).

Summary and conclusion

The 2014 Clinical Trial Regulation is still based on a two-tier system without ensuring patient involvement in the assessments. Our study demonstrates advantages of combining two-tier assessments of clinical studies into a single assessment. The assessments in the two projects were performed in an integrated manner (including scientific, patient-oriented, and ethical or safety aspects), and provided a combined ethical and legal evaluation of the research process. This is reflected by the type of issues involving ethics, safety, methodology, explanation, lay communication and feedback of results. The assessments were time-efficient (delivery of advice within 3-4 weeks) and devoted to patients (up to 50% active patient involvement in the assessments). Therefore, our examples support how ethics and safety assessments can be organised as a single assessment in the current 2014 EU clinical trial regulation[10] and including patient perspectives.

Although we examined only two studies restricted to respiratory diseases, ethical or safety assessment of all clinical studies may be organised in a similar way. For legal ethics committees (or competent authorities) it would imply the organisation of its members from a (European) pool of disease-related specialists and patients. Commitment should however not be compromised by providing incentives for members apart from reimbursement of expenses. We emphasise that the single integration of the different perspectives, the obligation to have patients as members of the ethics committee,[7,14] and the collaborative development of appropriate tools to engage all members of a legal ethics committee or competent authority need to be established for research ethics assessments in current medical research.

Acknowledgments

This study was carried out on behalf of the U-BIOPRED consortium (www.europeanlung.org/en/projects-and-research/projects/u-biopred/who-is-involved/project-members) and the PRO active consortium (www.proactivecopd.com/about/advisory boards), including principal investigators, ethics boards, the safety monitoring board and patient input platforms as stated on these websites. We acknowledge review and type-editing by dr. P.D. Powell (European Lung Foundation, Sheffield, UK) and prof. dr. P.J. Sterk (Academic Medical Center, Amsterdam, NL). The U-BIOPRED study is funded by Innovative Medicines Initiative Joint Undertaking (IMI-JU) grant #115010 and the PRO active study is funded by IMI-JU grant #115011. The sponsor IMI has no role in this study or in study design, data collection, analysis or interpretation, the writing or submission of this paper.

Conflicts of interest

Authors declare that there is no conflict of interest.

References

1. European Union. *Clinical Trials Directive 2001/20/EC*. European Union: Brussels, Belgium; 2001. 1–11 p.
2. EC consultation on EU clinical trial directive. *Summary of responses*. EC: Brussels, Belgium; 2001. 1–16 p.
3. ICREL. Impact on clinical research of European legislation. EFGCP: Brussels, Belgium; 2008.
4. Angell E, Sutton AJ, Windridge K, et al. Consistency in decision making by research ethics committees: a controlled comparison. *J Med Ethics*. 2006;32(11):662–664.
5. Fuchs M, Heyer M, Fischer N, et al. Draft Final Report: Provision of Support for Producing a European Directory of Local Ethics Committees (LECs). EC contract no SAS5-CT-2002-30047 Bonn. The Institute of Science and Ethics; 2005.
6. Kenter MJ, Cohen AF. Re-engineering the European Union Clinical Trials Directive. *Lancet*. 2012;379(9828):1765–1767.
7. Neitzke G. Patient involvement in clinical ethics services: from access to participation and membership. *Clin Ethics*. 2009;4(3):146–151.
8. Teunissen T, Visse M, de Boer P, et al. Patient issues in health research and quality of care: an inventory and data synthesis. *Health Expect*. 2013;16(4):308–322.
9. Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet*. 2014;383(9912):166–175.
10. *European Union (EU) Clinical Trials Regulation 536/2014*. Brussels: EP and the Council; 2014.
11. Goldman M. Public-private partnership need honest brokering. *Nat Med*. 2012;18(3):341.
12. http://www.ubiopred.eu
13. http://www.proactivecopd.com
14. Staley K. Lay REC members: patient or public? *J Med Ethics*. 2013;39:780–782.
15. Rari E, Fournier V. Strengths and limitations of considering patients as ethics 'actors' equal to doctors: reflections on the patients' position in a French clinical ethics consultation setting. *Clin Ethics*. 2009;4:152–155.
16. U-BIOPRED advisory boards – descriptions, charters and appraisal and monitoring criteria.
17. Teunissen GJ, Visse MA, de Boer WI, et al. Structuring patients advocates´ and evaluation of health research and quality of care. *J Participat Med*. 2013;5:320–330.
18. Supple D, Roberts A, Hudson V, et al. From tokenism to meaningful engagement: best practices in patient involvement in an EU project. *Research Involvement and Engagement*. 2015;1:12.