Ethical narrative

Setting-up a multi-center human research: Systematic observation during a Swiss clinical trial

Verena Gotta[a,b], Laure Vallotton[c], Thierry Buclin[a], Nicolas Widmer[a]

a Division of Clinical Pharmacology, Service of Biomedicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland
b School of Pharmaceutical Sciences, University of Geneva and University of Lausanne, Switzerland
c CTU Lausanne – Centre de Recherche Clinique de la Faculté de Biologie et de Médecine; Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland

Clinical trials aim at assessing the effectiveness and safety of drugs, medical devices, medical interventions (incl. surgery) and laboratory tests intended for human use. They are necessary to avoid scientifically unsubstantiated medical approaches and are therefore an essential tool to build up evidence-based medicine. Moreover, they represent the best way to evaluate options for unmet clinical needs. Ethical guidelines for medical research involving human subjects have mainly been established since the end of Second World War in response to the scandalous clinical experiments conducted at that time [1]. The necessity of studies approval by independent ethics committees (ECs) is nowadays undisputed to protect the rights, safety and well-being of study participants. Furthermore, ECs contribute to ensure the adequacy of the investigators, as well as of the study procedures, documents and facilities.

Investigator-initiated multicenter trial

We launched an investigator-initiated clinical trial to evaluate the potential benefit of pharmacokinetic-guided dosage individualization (therapeutic drug monitoring; TDM) of the already marketed anticancer drug imatinib for chronic myeloid leukemia (CML) patients followed in public and private sectors [2]. While *retrospective* studies had already suggested that patients under imatinib could benefit from dose individualization, the study was initiated to *prospectively* establish scientific evidence for the routine application of TDM in clinical practice. It addressed hereby also the ethical question of empirical dosing modifications possibly induced by poorly evaluated TDM use, as outlined by the FDA in a warning letter to the manufacturer [3].
Throughout the study, we recorded the amount of work and resources that were consecrated to formal observance of regulatory directives applicable to the ethical evaluation of this trial.
Because CML is a rare disease [4], patient recruitment throughout Switzerland was considered necessary to reach the statistically required number of patients for a sufficiently powered study. The study was thus designed as a multicenter trial, with a randomized controlled allocation procedure. Co-investigators were involved in the cantons of Vaud, Geneva, Lucerne, Basel, Bern, Ticino and Thurgau. Our planning was to have the study first approved by the local EC of the coordinating center (Lausanne, Vaud), to subsequently notify the study to the Swiss Agency for Therapeutic Products (Swissmedic) and finally to obtain approval by 11 out of 12 remaining cantonal ECs in a simplified procedure – as 2 regulatory authorities had initially evaluated the study. Thus, we analyzed requirements and evaluation procedures of the 12 involved ECs with associated costs. The time elapsed until approvals and the different requirements and operational procedures were summed up and compared. Queries risen before study release were systematically listed.

Evaluation of the process burden

After a first conditional approval in 02/2009, the final approval by the local EC of the coordinating center (Lausanne, Vaud) was obtained in 03/2009. Thereafter, the protocol was submitted to Swissmedic (04/2009), who did not consider necessary its notification, because it was not aiming at investigating the drug itself (already commercialized since 7 years), but only its blood concentration monitoring (05/2009). In the meantime the patient and physician information documents, as well as the protocol summary, were translated from French to German, entailing modifications also in the French version after the revision of German-speaking co-investigators. As this led certainly to improvements in the overall documentation, these final documents were resubmitted to the local EC of the coordinating center (06/2009) to obtain harmonized documents applicable throughout Switzerland. The accepted revisions (06/2009) were subsequently submitted in 07/2009 to 5 considered leading ethics committees (Lucerne, Zurich, Bern, Basel, Geneva) and in 09–10/2009, together with an additional Italian translation, to the 6 remaining cantonal EC (St. Gallen, Thurgau, Aargau, Neuchâtel, Ticino, Valais). Our study ended in 08/2012 and the results were recently published [5].
Including the initial submission for first local study approval, the 12 protocol submissions resulted in one

French version of the patient information and consent form, one Italian and five different German versions because of specific requirements issued by the German-speaking ECs. The number of dossiers required was between 1 and 18 copies; one EC additionally required a CD (Table 1). A total of 4300 pages (printing costs: ~170 CHF, paper weight: 12 kg, posting costs: ~120 CHF) were required to meet the initial local EC requirements (revisions and annual reports not included). Meeting frequency of the local ECs was unknown for one commission and ranged for the others between 2 weeks and 2 months. Study approval was the decision of a chairman, a subcommission or the full commission, with 1 to 13 members having generally been implicated in the decision process, while in 3 cases the number of involved persons was unknown. The evaluation work was invoiced by 0 to 1000 CHF (median: 750 CHF, total: 9200 CHF). The fees of second appraisals exceeded partly the costs for receipt of first approval. Time from submission to first feedback took 2 to 75 days (median: 28 days) and time to final approval 14 days to 6.5 months (median: 35 days; last approval in 04/2010). A standard formulary resuming the evaluation process with a reminder of the investigator's duties was sent with the approval by 9 ECs, two enclosed additionally an own formulary to report the annual study progress. Not considering the revisions asked during first study evaluation by the EC of the coordinating center, direct approval without any further objections was issued by 5 local ECs, including the 3 ECs of the French-speaking part of Switzerland. The other 6 involved local ECs from the German and Italian part raised 38 queries in total before study release, out of which investigators rejected 3. The number of persons implicated in the evaluation process was not correlated with the amount of fees or the number of queries expressed. One EC (Neuchâtel including the cantons Fribourg and Jura) was about to be dissolved at time of submission of the annual report.

Addressed requirements and recommendations are summarized in table 2. The majority (53%) consisted in formal objections regarding wording and declared date of revised versions in patient information, leading to 7 different final versions approved. During the study course, 2 EC had to be regularly updated on regional onco-hematologists in charge of patients included in the study. A reference contact person at the principal hospital center of the concerned canton was necessary to declare in 3 cantons.

To the best of our estimation, submission tasks roughly employed an investigator half-time over about 6 months. This evaluation does not include further administrative operations related to the set up of the trial (financial aspects, study organization and documentation, database set-up, etc.).

Table 1: Heterogeneity in protocol evaluation procedures of 12 ECs in Switzerland*

Number of dossiers required	1–18
Number of EC members involved in decision	1–13 (unknown in 3 ECs)
Charges	0–1000 CHF, total: 9200 CHF
Direct approval without any queries	by 5 EC
Recommendations & Requirements	by 6 EC (encompassing 38 queries)
Standard response formulary	9 out of 12
Frequency of EC meetings	24 per year – 6 per year
Time from submission to first consideration	–75 days (median: 28 days)
Time from submission to final approval	14 days–6.5 months (median: 35 days)
Total number of pages required (printing costs)	4300 pages (~172 CHF)
Total number of paper copies (kg, posting costs)	2400 pieces of paper (~12 kg; ~120 CHF)

*Revisions and annual reports not included

Table 2: Queries raised by 6 out of 11 ECs

Type of query	[%] of queries	Details (number of such queries)
Formal objections regarding wording and date declaration of revised versions in patient information	53%	Foreign wording, expression (8 + 8 due to translation) Date correction (2) Addition of the logo of local participating hospital center (1) Separate consent form (study and genetic analysis) (2)
Miscellaneous requests, remarks and recommendations, which did not concern the study protocol itself	29%	Request of regular information on local recruiting physicians (2) Request of nomination of a formal local contact person (3) Recommendation to register the trial (2) Request for a copy of industrial contract (1) Clarification of the institution being the sponsor of the study (1) Request for a consent to use the data of non-study participants (1) Request to consider a financing of costs associated with dose increase by manufacturer (1)
Content-related objections regarding patient information and consent form	13%	Request to declare financial support (1) Request to clarify study procedure with regard to data confidentiality (1) Request to declare the use of data in case of study withdrawal (1) Request to remove discussion of insurance costs associated with the study (1) Request to insert contact details for cantonal pharmacy (2)
Clarifications pursuant to GCP requirements	5%	Clarification of insurance coverage (2)

Overall perspective

The review of our protocol by several ECs has hopefully resulted in better understandability of the patient leaflet, since the majority of queries concerned this document (>50%) and has reduced inconsistencies due to

translations. Still, the cost/benefit ratio for these improvements seems questionable, if one considers that it employed 3 months of full-time work by a trained investigator and cost almost 10 000 CHF. Administrative burden and heterogeneous regulatory requirements for multicenter studies have already been addressed as important problems and risks for academic, as well as industrial initiated clinical research [6]. This is not only the case in Switzerland [7], but also in other European countries [8–10] – despite application of the same rules of the EU Directive 2001/20/EC. This complex time-consuming experience reduces the willingness of investigators to participate in multicenter studies [11] and can impede the realization of clinically, scientifically and ethically important research projects. The procedure of multiple submissions is indeed costly, without essentially improving the protection of study participants. Additionally, it complicates the handling of resultantly heterogeneous study documents. At the start of our study, we were facing with 7 different versions of patient information for Switzerland, which may also have confused physicians and patients involved in the study. Depending on the potential benefit for patients to participate in a study, this procedure may delay not only the research projects themselves, but also sometimes jeopardize the interests of patients [6, 12].

In Switzerland, the necessity of ethical surveillance of clinical research on drugs by independent EC was advised since 1970 by the Swiss Academy of Medical Sciences and became mandatory for new drug treatments in 1995. It was further reinforced by the Ordinance on Clinical Trials of Therapeutic Products (OClin) in 2002 [13]. The total number of ECs fell progressively from over a hundred in the early 1990s [14] to 13 at time of our initial protocol submission. They are each responsible for 1 to 6 cantons and partly organized in up to 5 specialized sub-committees. The meeting frequency for evaluation of submitted protocols varies considerably between ECs (6 to 24 times per year), and depends probably mainly on the research activity of the concerned region. In fact, the average number of clinical research projects submitted for certain cantons varies between 15 (e.g. Schaffhausen) and more than 500 per year (Zürich) [14]. This may have an important influence on the experience and routine practice of ECs. Aware of heterogeneity in research protocol evaluations across Switzerland, Swiss ECs allied in 2005 to form the Association of Research Ethics Committees (Arbeitsgemeinschaft der Ethikkommissionen, AGEK) aiming at improving cooperation between local ECs and harmonizing evaluation procedures. However, as our example illustrates it, there still remained a clear need for harmonization about 10 years after its foundation.

Thus, the recent entry into force of the new federal law on research in humans (Humanforschungsgesetz [HFG], Loi relative à la recherche sur l'être humain [LRH], Legge sulla ricerca umana [LRUm]) [15] and its three linked ordinances were welcomed, as they opened the way to mutual recognition of ECs and procedures for multicenter studies. The EC of the coordinating center is now defined as the leading committee that obtains the opinion of other ECs, instead of the investigator personally, as was previously the case.

In our opinion, harmonization should not mainly result in a further reduction of the total number of ECs in Switzerland as currently observed. Regional infrastructural or sanitary organizational differences may have to be considered for local study procedures. As well, perception of ethics may regionally differ due to local cultural factors. The heterogeneity in the perception of appropriate study documentation in our study (direct acceptance without any queries by EC from the French-speaking part, more detailed evaluation by several ECs from the German-speaking part) is intriguing. It illustrates however the necessity to collaborate closely with ECs from all parts of Switzerland: the complete 4-lingual study documentation (the protocol usually being written in English) already represents a challenge for researchers in a small country like Switzerland. The harmonization procedure should additionally take into account the overall increase in clinical research activity [16] and the resulting increased workload for ECs in the future.

As previously advocated, the conduct of a clinical trial to meet the increased quality requirements, demands more and more professional management, know-how and manpower [17]. The recent development of clinical trial and research units (CTU/CRU) in university hospital centers should therefore be further advanced. Six Swiss units are currently supported by the clinical trial units program of the Swiss National Science Foundation, with the objective to achieve harmonized, internationally accepted quality standards for the conduct of academic and commercial "patient-oriented" clinical research.

Further comparative systematic evaluation of these processes in the next years will be warranted to monitor the practical effects of the new law and ordinances, and could also be useful to other countries and regulatory systems. Finally, harmonized electronic application forms and database will be created, preferably compatible with other regulatory bodies (e.g. Swissmedic) and European countries. This kind of system, which is already developed in the UK [9], could increase transparency of trial evaluation, improve communication, reduce administrative burden for researchers, paper consumption and costs, and thus contribute to encourage academic multi-center clinical research in Switzerland.

Acknowledgements

The present work was partly funded by the Swiss National Science Foundation (Bern, Switzerland) through the Nano-Tera Initiative (ISyPeM project). The develop-

ment and application of imatinib blood measurement at the Division of Clinical Pharmacology, Centre Hospitalier Universitaire Vaudois and University of Lausanne (Lausanne, Switzerland) has also received an unrestricted grant from Novartis Pharma Schweiz (Bern, Switzerland).

Correspondence
Prof. Thierry Buclin, MD
Division of Clinical Pharmacology
Centre Hospitalier Universitaire Vaudois and
University of Lausanne
Rue du Bugnon 17
CH-1005 Lausanne
Tel.: +41 (0)21 314 42 60
Fax: +41 (0)21 314 42 66

E-mail: Thierry.Buclin[at]chuv.ch

References

1. Bosnjak S. The Declaration of Helsinki – the Cornerstone of Research Ethic. Arch Oncol 2001; 9(3): 179–84.
2. Buclin T, Widmer N, et al. Who is in Charge of Assessing Therapeutic Drug Monitoring? The Case of Imatinib. Lancet Oncol 2011; 12(1): 9–11.
3. US Food and Drug Administration. Re: NDA 021588 Gleevec (imatinib mesylate) - Warning Letter. April 4, 2010. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm259229.htm (accessed July 10, 2013).
4. Orphanet. Orphanet: Chronic Myeloid Lleukemia. http://www.orpha.net. (accessed July 10, 2013).
5. Gotta V, Widmer N, et al. Clinical usefulness of therapeutic concentration monitoring for imatinib dosage individualization: results from a randomized controlled trial. Cancer Chemother Pharmacol 2014; 74(6): 1307–19.
6. Horrobin DF. Are Llarge Clinical Trials in Rapidly Lethal Diseases Usually Unethical? Lancet 2003; 361(9358): 695–7.
7. Hernandez R, Cooney M, et al. Harmonisation of Ethics Committees' Practice in 10 European Countries. J Med Ethics 2009; 35(11): 696–700.
8. Russ H, Busta S, et al. Evaluation of Clinical Trials by Ethics Committees in Germany: Experience of Applicants with the Review of Requests for Opinion of the Ethics Committees – results of a Survey Among Members of the German Association of Research-Based Pharmaceutical Companies (VFA). Ger Med Sci 2009; 7: Doc07.
9. Smajdor A, Sydes MR, et al. Applying for Ethical Approval for Research in the United Kingdom. BMJ 2009; 339: b4013.
10. Hearnshaw H. Comparison of Requirements of Research Ethics Committees in 11 European Countries for a Non-invasive Interventional Study. BMJ 2004; 328(7432): 140-1.
11. Maskell NA, Jones EL, et al. Variations in Experience in Obtaining Local Ethical Approval for Participation in a Multi-centre Study. QJM 2003; 96(4): 305–7.
12. Glasziou P, Chalmers I. Ethics Review Roulette: what Can We Learn? BMJ 2004; 328(7432): 121–2.
13. Antwort des Bundesrates vom 03.12.2004. Hindernisse für klinische Studien in der Schweiz (Anfrage 04.1105). http://www.parlament.ch/d/suche/seiten/geschaefte.aspx?gesch_id=20041105 (accessed July 10, 2013). Die Bundesversammlung – Das Schweizer Parlament, Curia Vista – Geschäftsdatenbank.
14. European Network of Research Ethics C. National Information: Switzerland. http://www.eurecnet.org. (accessed July 10, 2013).
15. Bundesamt für Gesundheit. Verfassungsartikel über die Forschung am Menschen (Art. 118b BV) vom 7. März 2010. http://www.bag.admin.ch. (accessed July 10, 2013).
16. Amstad H. Auf der Suche nach Versuchspersonen für klinische Versuche. 2002. pp. 2216–9.
17. Salzberg M, Muller E. Quality Requirements in Clinical Studies: a Necessary Burden? Swiss Med Wkly 2003; 133(31-32): 429–32.