

Analysis of enforcement by the approval authorities prior to the introduction of the Human Research Act (HRA)

Summary of the report prepared for the Human Research and Ethics Section of the Federal Office of Public Health

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INTRODUCTION

The Federal Act on Research involving Human Beings (Human Research Act, HRA), which came into force on 1 January 2014, specifies the ethical, scientific and legal requirements which human research has to meet. Under Art. 61 of the HRA, the Federal Office of Public Health (FOPH) is required to assess the effectiveness and appropriateness of the Act with regard to protecting the dignity and privacy of human research subjects, as well as the general conditions for research. To provide a basis for the planned subsequent evaluation of enforcement of the HRA, the situation existing in 2013 – prior to the introduction of the HRA – was investigated in this study.

Based on data and document analysis and guided interviews with representatives of nine ethics committees, three representatives of Swissmedic, three representatives of the FOPH and a representative of the Federal Office for the Environment (FOEN), the structures, processes and outputs of enforcement in the area covered by the HRA were investigated. Just as enforcement and the activities of the various approval authorities were characterised by a high degree of diversity, so also the quality of the data analysed in this study varied widely. This needs to be borne in mind when comparisons are made between individual approval authorities. Below, the key questions considered in the analysis of existing structures, processes and outputs are answered by way of a summary.

ANALYSIS OF EXISTING STRUCTURES

What form do existing enforcement structures take? How are the relevant approval authorities organised?

In 2013, approval authorities at the cantonal level took the form of 13 ethics committees. Their internal organisation varied: for the nine committees included in the study, the number of members ranged from 7 to 48. Some of the ethics committees had several subcommittees, while others were reconstituted for each meeting from a pool of members. Others again reviewed research applications in plenary sessions and had correspondingly fewer members. Four committees made the number of members participating dependent on the type of procedure (regular or simplified). On average, the members had 25–30 years' professional experience. Accounting for 45% of all members, medical professionals were the largest of the roughly ten professional groups represented. Patients were also explicitly represented on two committees.

At the federal level, various divisions and sections of Swissmedic, the FOPH and the FOEN were responsible for enforcement in the area covered by the HRA. At Swissmedic, the Clinical Trials Division reviewed applications for studies involving medicinal products, the Medical Devices Division was responsible for trials of medical devices, and applications for trials of transplant products were reviewed by the Transplant Products Division. Where appropriate, opinions were provided to Swissmedic by the Radiological Protection Division, the Transplantation and Reproductive Medicine Section and the Biological Safety and Human Genetics Section of the FOPH, and by the Biotechnology Section of the FOEN. Within the federal approval authorities, a small number of people were responsible for reviewing applications, with most reviewers being biologists or medical professionals.

In 2013, applications for clinical trials were reviewed in a sequential process, first by the ethics committees and then by Swissmedic. Both authorities evaluated all aspects of the applications autonomously and independently of each other. In practice, however, the ethics committees focused in particular on ethical and scientific aspects, in the knowledge that compliance with Good Clinical Practice (GCP) guidelines and legal aspects were reviewed in detail by Swissmedic. For trials involving transplant products, radioactive sources or genetically modified or pathogenic organisms, Swissmedic additionally sought an opinion from the appropriate section of the FOPH or FOEN.

What are the costs of enforcement?

With the data available, it was not possible for the costs of enforcement to be precisely calculated. This is because certain costs were borne by third parties and could not be explicitly documented. In 2013, the costs reported by ethics committees amounted to between CHF 20,000 and 1.36 million. The costs for all the ethics committees combined came to CHF 4.27 million. Expenditures comprised personnel costs, attendance fees and infrastructure costs, with personnel costs accounting for the largest proportion. Since the reported costs did not coincide with the actual costs for all committees – e.g. because personnel or infrastructure costs were charged to other budgets – comparisons between committees are only possible to a limited extent.

The costs of enforcement by the federal approval authorities in 2013 could only be roughly estimated on the basis of the number of hours worked, since the costs are not separately recorded. Overall, the costs incurred by the federal authorities came to around CHF 3.1 million. In 2013, the total reported costs of enforcement in the area covered by the HRA in Switzerland thus came to around CHF 7.4 million. The actual costs are, however, likely to be higher.

What is the ratio of costs to outputs?

To measure the ratio of costs to outputs, the total reported costs of the ethics committees were divided by the number of new applications processed. Despite this normalisation, comparisons between ethics committees can only be made to a limited extent because firstly – as mentioned above – the reported costs did not always coincide with the actual costs and, secondly, the number of amendments processed, which varied markedly from one ethics committee to another, could not be taken into account in the calculations, since not all committees had the relevant data. Subject to these qualifications, the costs for the ethics committees per new application processed came to CHF 606–2,810 in 2013. The smaller ethics committees tended to report lower costs than the larger committees in cantons with a university hospital or a strong pharmaceutical industry presence. Apart from the methodological factors mentioned above, the differences between the ethics committees can presumably be attributed primarily to differences in the complexity and number of applications processed and to the variation in personnel costs.

At the federal level, the costs per new application cannot be determined, since Swissmedic's costs arose to a significant extent from the inspections performed, and therefore normalisation with the number of new applications processed does not yield meaningful figures.

How are the approval authorities financed?

The cantonal ethics committees were financed primarily through fee income. In 2013, the fees earned by committees ranged between CHF 17,500 and 870,000. In addition, certain committees received basic funding or deficit guarantees from the canton. In many cases, the ethics committees' total reported costs were higher than the available financing. For the ethics committees concerned, the shortfalls were presumably covered by the deficit guarantees or the release of reserves. However, a conclusive explanation for the difference between costs and financing could not be found.

There were substantial differences between individual ethics committees' fee regulations. The regulations distinguished between different types of procedure (normal procedure, simplified procedure, multicentre studies,) and study funding (industry-funded, academia-funded/investigator-initiated, non-commercial third party-funded). The fees for reviewing new applications were between CHF 0 and 5,000; the highest fees charged were for industry-sponsored studies, followed by investigator-initiated studies and student projects or non-commercial studies. Fees for amendments were lower, ranging from CHF 0 to 750.

The federal approval authorities were largely financed through the federal budget; the financing of enforcement in the area covered by the HRA was not separately reported. For Swissmedic, further sources of financing were income from levies on sales of medicinal products and the processing fees charged by the agency.

How are the approval authorities supervised and what guidelines do they have to follow?

In most cantons, the cantonal government or a health department official was responsible for supervision of the ethics committees in 2013. No directives were issued, and no inspections of approval authorities were performed.

ANALYSIS OF EXISTING PROCESSES AND OUTPUTS

How are the enforcement activities specified in the HRA carried out?

In 2013, the ethics committees mainly carried out reviews of applications. In addition, they provided applicants with information about submission procedures and advice on legal and substantive questions regarding applications. The control function, including the imposition of sanctions, was primarily exercised by Swissmedic in the course of its inspection activities. The ethics committees lacked the resources to perform inspections themselves. Reviews of applications also accounted for the bulk of the work performed by the federal approval authorities. At the federal level, information was once again provided primarily by Swissmedic – the FOPH and FOEN had little direct contact with researchers, as the evaluation process was coordinated by Swissmedic. In 2013, the enforcement activities of the cantonal and federal approval authorities were not centrally coordinated. If necessary, however, the authorities communicated informally with each other, e.g. in the event of queries on specific applications. For ethics committees and Swissmedic, the authorities' websites were the most important channel for communication with the public. Here, all the information required for the submission of applications was made available. In addition, both ethics committees and Swissmedic gave presentations at various institutions in order to inform applicants about the requirements for submission of applications. The relevant units of the FOPH and the FOEN engaged in little or no PR work, as their opinions were coordinated via Swissmedic and they were thus not directly in contact with applicants.

What/how many outputs specified in the HRA and the related ordinances are delivered?

In 2013, the ethics committees reviewed a total of 2,306 new applications (varying from 33 to 621 per committee) and 1,637 amendments (between 10 and 828 per committee); amendments were not (or not fully) recorded by two committees. Most of the applications (60%) concerned investigator-initiated studies; 37% concerned multicentre studies, with just under half of these being evaluated under the newly introduced lead ethics committee procedure. The ethics committees also provided applicants with information in numerous cases and – in swissethics working groups – developed standard submission templates with regard to the HRA.

The federal approval authorities processed a total of 275 new applications (Swissmedic 266, FOPH and FOEN 9) and 3,608 amendments. The reasons for the difference in the number of amendments processed by the ethics committees and by Swissmedic could not be determined. More than half (54%) of the studies evaluated by the federal approval authorities were funded by an industry sponsor. Among the federal authorities, information was provided chiefly by Swissmedic. In addition, Swissmedic performed 23 inspections in 2013 (excluding clinical trials with transplant products).

How is the formal review of applications conducted?

Applications are reviewed by ethics committees in various ways. Most of the ethics committees used a system involving delegation, while in some cases all applications were discussed in plenary sessions without preparations being undertaken separately by individual members. The ethics committees sought to ensure that individuals with expertise in different areas were involved in the evaluation. Six of the nine ethics committees investigated had internal frameworks specifying criteria for the review of applications; these were employed with varying frequency. As ethics committee members served in a part-time capacity, conflicts of interest could arise; these were generally resolved by recusal provisions.

Within the federal approval authorities, applications were reviewed by employees of the units concerned. The relevant sections of the FOPH and the FOEN provided opinions for Swissmedic. The various aspects of applications were evaluated by the authorities sometimes with and sometimes

without predefined criteria; this was partly due to the fact that applications for highly specialised trials were only standardised to a limited extent and were thus scarcely comparable.

How long does it take for applications to be reviewed?

In 2013, the duration of the review of applications was only systematically recorded by four of the nine ethics committees. According to this data and the assessments of respondents from the other five committees, the average processing time (excluding clock-stops) for all ethics committees was 21 days (median 23 days). Among the nine ethics committees, the average evaluation time ranged from 13 to 30 days. No comprehensive explanation could be found for the differences in evaluation time. The hypothesis that the evaluation time is longer for committees with large numbers of new applications than for those with small numbers could not be confirmed. Likewise, the processing time for committees in locations with university hospitals did not appear to differ systematically from smaller ethics committees. A demonstrable effect on the maximum duration of processing was only seen in the case of committees with a fixed meeting frequency.

For the federal approval authorities, according to respondents' assessments, the duration of the review of applications was between 7 and 30 days (mean 19.5 days, median 21.5 days).

What is the status of harmonisation between the various approval authorities?

The harmonisation of procedures is newly specified in the HRA (Art. 49). Before the HRA came into force, harmonisation was not an explicit goal. As ethics committees in 2013 did not apply uniform evaluation criteria and substantial differences existed, for example, with regard to fees or evaluation times, it can be assumed that harmonisation was rather limited prior to the introduction of the HRA. However, this cannot be demonstrated by data. Looking ahead, two measures initiated in 2013, which will contribute to future harmonisation, were mentioned in particular by the ethics committees interviewed: firstly, the application – still voluntary in 2013 – of the lead ethics committee procedure for multicentre studies and, secondly, closer collaboration and the joint development of templates in swissethics working groups.

In 2013, as the various federal approval authorities were each responsible for different aspects of the review of applications, harmonisation between these authorities and with the ethics committees was not relevant.