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# The role of Clinical Trial Units in investigator- and industry-initiated research projects

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## Summary

Six multidisciplinary competence centres (Clinical Trial Units, CTUs) in Basel, Berne, Geneva, Lausanne, St. Gallen and Zurich provide professional support to clinical researchers in the planning, implementation, conduct and evaluation of clinical studies. Through their coordinated network, these units promote high-quality, nationally harmonised and internationally standardised clinical research conduct in Switzerland. We will describe why this network has been established, how it has been successful in stilling the growing need for clinical research support, which training and education opportunities it offers, and how it created national awareness for the still-existing hurdles towards clinical research excellence in Switzerland. Taking the CTU Basel as an example, we show that a considerable number (25%) of the studies submitted for regulatory approval in 2013 were supported by the CTU, decreasing the number of findings in ethics reviews by about one-third. We conclude that these achievements, together with a Swiss national funding model for clinical research, and improved national coordination, will be critical factors to successfully position Swiss clinical research at the international forefront.

***Key words:*** *clinical research; clinical trial unit; academic research; patient-oriented research*

## Need for more professionalism

Clinical studies are a prerequisite for advancing our understanding and treatment of disease. Their complexity and the regulatory requirements, however, have significantly increased over the last few years, requiring an ever-rising level of scientific, methodological, regulatory and organisational know-how to be able to perform high-quality research. Global biomedical and public health research involves billions of dollars and millions of people, resulting in an estimated 1 million research publications per year [1]. At the same time, less than 20% of drugs entering testing in humans (phase I) successfully reach the proof of efficacy and safety (phase III) [2]. Chalmers and Glasziou [1] describe the causes of "waste" in biomedical research occurring at four successive stages: the choice of research questions; the quality of research design and methods; the adequacy of publication practices; and the quality of reports of research. If Phase III is reached, one out of four randomised controlled trials is discontinued, mainly owing to insufficient recruitment of participants [3].

In Switzerland the quality of clinical research has been of concern for more than 30 years. In the 90s, there were complaints that patient-oriented clinical research in Switzerland was not keeping pace with the high quality of basic biomedical research [4, 5]. In 1994, the Working Group for Science and Research (Gruppe für Wissenschaft und Forschung, GWF) decided to commit to the resolution of the underlying structural issues [6]. Around the same time, similar concerns were raised in Europe and the United States leading to the launch of the International Campaign to Revitalise Academic Medicine (ICRAM) [7], a global initiative that is committed to fostering a debate about the future of academic medicine. The campaign arose because of a persistent concern that academic medicine is in crisis around the world. At a time of increasing health burden, poverty, globalisation, and innovation, many have argued that academic medicine is nevertheless failing to realise its potential and global social responsibility.

In 2002, the Swiss Science and Technology Council SWTR (now Swiss Science and Innovation Council, SWIR) issued practical recommendations for further improvement of clinical research in Switzerland. The three key messages included [8]: (1) the development and training of young clinical academics should be promoted, e.g. in the form of training grants financed by the Swiss National Science Foundation (SNSF); (2) training, teaching and research at university hospitals should be separated from service provision and therefore financed by the university the hospitals are affiliated with; and (3) attractive positions (20% clinical work, 80% research) should be created, with the possibility to commit to research short term (2–4 years), mid-term, or permanently. In addition, the SWTR concluded that even if these aspects are of importance individually, the critical factor for success will be the national coordination of Swiss patient-oriented research.

Stimulated by the SWTR recommendations, the SNF recognised the need for nationally coordinated specialised

competence centres, which would support clinical researchers in the planning, setup, conduct, and analysis of their clinical research projects in accordance with international standards and guidelines. Between 2007 and 2008, the SNF therefore supported the initial funding of so-called Clinical Trial Units (CTUs) at the university hospitals in Basel, Berne, Geneva, Lausanne and Zurich, and at the Cantonal Hospital St.Gallen [4]. The initial SNF funding served to establish and expand CTU infrastructure, with the prerequisite that all CTUs will be co-financed by their affiliated institutions (e.g. university, hospital). Furthermore, they should be able to generate own revenue through activities such as service provision, courses or the collaboration with industry.

## CTUs as interdisciplinary competence centres

After the successful completion of the build-up phase, CTUs nowadays act as interdisciplinary competence centres for clinical research at their local – and surrounding – academic institutions. Their main function is to support efficiently the clinical departments of university hospitals in the planning and execution of patient-oriented clinical research projects (both investigator and industry-initiated trials) and to advance the quality of clinical research. They respond to the growing need for support in different areas of study planning and conduct, create awareness of the challenges still existing at a national level, and thereby foster a more favourable environment for academic clinical research in Switzerland. By making use of the services provided by the coordinated CTU network, scientists support the advancement in excellence and support the competitive positioning of Swiss clinical research at an international level.

Although all CTUs are committed to the same mission, they may differ in specific aspects or areas of expertise. These specifics are often determined by the local environment, i.e. the pre-existing research infrastructure, expectations or needs of local research groups and strategic decisions as to clinical research focuses (i.e. oncology, cardiology) of the medical faculties. In general, the CTUs' fields of activity cover the following areas of expertise [15]:

- advising researchers on designing clinical research protocols, including methodological and statistical support;
- supporting researchers in the submission process of study dossiers to ethics committees and regulatory authorities;
- providing researchers with the methodological and logistical support required to perform clinical research (e.g. the recruitment of participants, technical support, access to investigator networks);
- conducting clinical research in collaboration with and on behalf of clinicians;
- providing training and education for principal investigators and clinical research staff.

To cover these areas, CTUs operate with broad teams of experts from different fields, including experts in research methodology, statistics, data management and project management, on site management and quality management. Initial consulting services as well as the set-up and maintenance of quality structures are usually funded by the home universities, and additional services are remunerated on a fee-for-service basis out of the investigators' research grants. These services are also available to external – i.e. non-university/hospital – customers. As the CTUs generally work with no profit margin, baseline core funding by affiliated institutions is always required.

## National coordination of CTUs

The primary aim of local CTUs is to improve research professionalism and quality at their home institutions. However, in line with the SWTR report [8], sustainable improvement of research quality in Switzerland will also critically depend on the national coordination of these local initiatives. With this in mind, the national coordination of clinical research infrastructures was one of the major goals of the SNSF. Therefore, in parallel to the build-up of the local CTUs, the SNF invested in the establishment of the Swiss Clinical Trial Organisation (SCTO) [16], which was conceived as the central cooperation platform for patient-oriented clinical research in Switzerland. Its objective is to competitively position Swiss clinical research in the international environment with respect to innovation and quality. To this end, the SCTO coordinates and facilitates the cooperation between the CTUs, mainly with respect to the areas of quality standards (i.e. definition and implementation of internationally recognised quality standards for the conduct of studies), the continued education and training coordination, and the facilitation of national and international multicentre clinical research [15]. Through the SCTO, the CTUs are also linked to other national and European initiatives, such as the Swiss Pediatric Network (SwissPedNet) [7], the European Clinical Research Infrastructure Network (ECRIN) [18] or the European Patient's Academy on Therapeutic Innovation (EUPATI) [19]. Furthermore, the SCTO acts as a connector between CTUs, regulatory bodies, ethics committees, industry and other stakeholders on a national level.

## Research projects and support at CTUs

In 2013, the six SNSF-funded CTUs actively contributed to more than 650 clinical research projects, over 70% of which were of academic origin [20]. Out of these academic projects, 60% were interventional trials with drugs or medical devices and 40% belonged to other types of studies, i.e. diagnostic trials, observational studies or cohort projects. In industry-sponsored trials, the percentage of drug- and device trials was significantly higher and amounted to roughly 80%. This is very well in line with the observation that most of the industry-sponsored projects are phase II or III registration trials with new drugs and devices. Although there is some variation in the ratio of academic:industry trials among the six CTUs, the predominance of academic trials holds true for all CTUs [20]. Furthermore, the type of support provided varied between academic and industry-sponsored trials. Amongst all CTUs, more than 50% of ser-

vices for academic trials were required in the early phase of study conception and planning, which relates to methodological and statistical support as well as help with regulatory submission. Another 20% were required during the completion phase of a study, relating to statistical support with data analysis. In contrast, industry-sponsored trials required 65% of the services during project set-up and conduct phase, which comprises support by study nurses and trial coordinators in the on-site management [20]. This is well explained by the fact that commercial study sponsors usually have their own research infrastructure but depend on well-trained on-site personnel to assure patient recruitment and management in line with the study protocol. In contrast, budget constraints in the academic setting do not often allow for the same amount of labour-intensive and costly services, such as monitoring, during later phases of a study.

## A closer look: the CTU Basel

As a representative example, we investigated the role of the CTU Basel in studies conducted in its catchment area. Therefore, we analysed all regular study submissions to the Ethics Committee of Both Basels (EKBB) in 2013, prior to the introduction of the new Human Research Act (HRA) and its ordinances We specifically chose this time period for our analysis as more recent data (i.e. from 2014) were not deemed representative owing to major changes and restructuration in the regulatory review system. Investigators, CTUs, as well as ethics committees had first to become acquainted with the new requirements, regulations and work processes.

According to the research law in 2013, regular submissions to ethics committees cover all studies that prospectively enrol patients. Of all 178 regular submissions to the EKBB in 2013 (including protocols from academia as well as from industry) the CTU Basel was involved in 46 (26%) (table 1). Not surprisingly, the CTU was predominantly involved in academic studies initiated by researchers at the University Hospital Basel. Forty-six percent of the investigators at the University Hospital Basel submitting an academic study to the ethics committee used the support provided by the CTU, in contrast with only 17% of all submitted industry sponsored projects. In about the same order of magnitude (14%), the CTU Basel was involved in studies from other academic institutions.

Interventional studies were slightly more often supported than observational studies and, overall, the CTU predominantly assisted medical device studies (78% of all submissions in Both Basel in 2013). Two-third of all submitted protocols of drug trials were sponsored by industry, but only 27% made use of CTU services.

Overall, the CTU Basel contributed to 271 studies in 2014 and to 212 studies in 2013 (table 2), which is a multiple of the 46 prospective studies newly submitted to the ethics committee in 2013. This difference in numbers can be explained by the fact that many of the supported projects received ethics approval in earlier years, were not subject to the regular submission process (i.e. retrospective studies), or were not followed up after initial consultation or sample size estimation.

Of the 212 studies that were supported by the CTU Basel in 2013, 128 studies made use of free consulting services and 159 used at least one contracted service (table 2). The average time the CTU spent on each project substantially differed from service to service. Of the 46 projects supported by the CTU Basel that were regularly submitted to the EKBB in 2013, all were supported by free consultation. In the planning and preparation phase before the initial submission to the EKBB (20 projects in 2013), all projects made use of consulting services whereas every second pro-

**Table 1:** Number and proportion of studies regularly submitted to the EKBB in 2013 which received support by the CTU-Basel, stratified by type of studies.

| | | Total number of study submissions to EKBB in 2013 | Studies with CTU support |
|---|---|---|---|
| Sponsor | | | |
| Industry sponsored studies | | 41 | 7 (17%) |
| Academic studies | University Hospital Basel | 61 | 28 (46%) |
| | Other academic institutions* | 76 | 11 (14%) |
| Type of studies† | | | |
| Interventional Study | | 76 | 24 (32%) |
| Observational Study | | 102 | 22 (22%) |
| Drug | Phase I | 12 | 4 (33%) |
| | Phase II | 14 | 4 (29%) |
| | Phase III | 12 | 3 (25%) |
| | Phase IV | 7 | 1 (14%) |
| | Subtotal drugs | 45 | 12 (27%) |
| Medical device | With CE | 6 | 5 (83%) |
| | Without CE | 3 | 2 (67%) |
| | Subtotal medical devices | 9 | 7 (78%) |
| Epidemiological study | | 17 | 2 (12%) |
| Basic research | | 14 | 4 (29%) |
| Other | | 93 | 21 (23%) |
| Total | | 178 | 46 (26%) |

CTU = Clinical Trial Unit; EKBB = Ethics Committee of Both Basels

* Including the University of Basel, the Swiss Tropical and Public Health Institute, the Psychiatric Clinic of the University of Basel etc.

† Categories for the type of studies are as indicated on the submission form of the EKBB

ject required statistical support (mostly sample size estimations).

We measured the impact of the CTU Basel services on the quality of study submissions. As a measure of quality we counted the number of findings by the ethics committee in the first submission. We only considered those projects that were supported by the CTU before the first submission (n = 20 out of 46) as investigators tend to submit studies initially without CTU support and only contact the CTU after experiencing difficulties.

Overall, the median number of findings was significantly reduced from 14 to 9.5 if the CTU Basel was involved with the provision of at least one of the services in the planning phase of a study (p-value: 0.02, Wilcoxon test). The reduction was most remarkable in the categories "general findings" and "formal aspects", where the median number of findings decreased from 3 to 2 and 9 to 4.5, respectively. The number of findings (median of 2) in the category "patient information and consent", however, was not affected.

We think that the broad expert opinion as reflected in the judgment of the EKBB is a limited, but valid, measure for the quality of the submitted studies. The main shortcoming of the used quality measure is that it considers only the study planning and not the conduct phase of a study. However, there is currently no established standard available for the quality improvement due to CTUs. SCTO and CTUs are aware of this shortcoming and have recently committed to defining performance indicators and standards, which should allow the quality improvement due to CTU services to be evaluated and benchmarked in the future.

## Training opportunities at CTUs

All parties involved in organising and supervising clinical research agree that investigators need adequate training to carry out their duties, which is one of the factors that fosters the development of high-quality clinical research. European initiatives such as the Innovative Medicines Initiative (IMI) [21], PharmaTrain [22] (an IMI programme on training in medicines development) and ECRIN have also joined forces to address this issue. The current qualification standards for investigators are generally vague and vary widely between European Union (EU) countries. Only Sweden, the United Kingdom, Switzerland, Hungary, and Lithuania require a Good Clinical Practice (GCP) certificate as a minimum regulatory requirement for researchers participating in clinical trials [23]. At the same time, clinical research has only been a marginal subject to undergraduate medical training in Europe.

Therefore, in addition to supporting specific research projects, the CTUs across Switzerland offer comprehensive investigator and study personnel training. All basic and advanced courses in GCP and related topics offered by the CTUs are officially recognised by the Swiss Agency for Therapeutic Products, Swissmedic and the Association of Ethics Committees (SwissEthics). In addition, all courses have a general accreditation of the Swiss Association of Pharmaceutical Professionals (Swapp) and the Swiss Society of Pharmaceutical Medicine (SGPM).

In 2012, more than 2,300 participants successfully completed a GCP course at one of the 6 SNSF-funded CTUs [20]. Some CTUs, such as the CTU Basel joined forces with their local ethics committees for investigator trainings, to more efficiently support researchers in understanding the current regulatory requirements and how to overcome the hurdles of regulatory submission.

Additionally, the CTUs have developed different postgraduate programmes best to serve the different needs of clinical research professionals such as study nurses and study coordinators, study managers and study physicians, clinical monitors and clinical trial assistants. The programmes may also serve those who wish to turn their careers towards clinical research. In addition, some CTUs offer courses in clinical research methodology and statistics, which specifically address senior clinical researchers who act as independent group leaders. These courses are often linked to other currently established educational programmes for researchers such as PhD or MD/PhD programs in clinical research. Such programmes, in combination with dedicated research time for clinicians, finally offer career opportunities in clinical research which were absent for decades.

## Impact of CTUs on research quality

In order to harmonise quality standards, all CTUs and the associated network Swiss Group for Clinical Cancer Research (SAKK) have jointly developed a quality policy. Therein, all units commit themselves to align their man-

**Table 2:** CTU support (number of services, total hours worked) of studies in general (2013/2014) and studies submitted to the EKBB (2013), stratified by type of service.

| | **2013** | | **2014** | | **CTU support of studies regularly submitted to EKBB in 2013** | | **CTU support *before* first submission to EKBB in 2013** | |
|---|---|---|---|---|---|---|---|---|
| | Services | Total hours | Services | Total hours | Studies | Total hours | Studies | Total hours |
| Consulting | 128 | 1,200 | 172 | 1,400 | 46 | 400 | 20 | 250 |
| Statistics | 85 | 3,200 | 91 | 3,600 | 15 | 300 | 10 | 150 |
| Data management | 37 | 2,000 | 54 | 3,800 | 10 | 800 | 0 | 0 |
| Monitoring | 37 | 1,500 | 39 | 2,200 | 10 | 700 | 0 | 0 |
| On-site management | 23 | 4,000 | 32 | 2,800 | 5 | 800 | 0 | 0 |
| Regulatory | 27 | 900 | 38 | 1,100 | 6 | 500 | 4 | 50 |
| Total number of services | 337 | | 401 | | 92 | | 34 | |
| Total number of paid services | 209 | | 254 | | 46 | | 14 | |
| Total number of studies | 212 | | 271 | | 46 | | 20 | |
| Total number of studies with paid services | 159 | | 187 | | 30 | | 14 | |

CTU = Clinical Trial Unit; EKBB = Ethics Committee of Both Basels

agement systems in accordance with applicable national and international regulatory requirements, the Good Clinical Pratice (GCP) Guidelines issued by the International Conference on Harmonization (ICH), with internationally acknowledged process-oriented standards for Quality Management Systems (QMS), with information security management (ISO 27001 Information Security Management – Specification With Guidance for Use), with the Guidelines for Good Clinical Data Management (Good Clinical Data Management Practices, GCDMP), and others [24]. Furthermore, the SCTO together with the CTUs developed Guidelines for Good Operational Practice, which should give guidance of how to apply the criteria of Good Clinical Practice in the academic setting. In conjunction with other common guidelines, such as the guidelines of Good Data Management Practice, the SCTO training and education policy and a set of common Standard Operating Procedures, these documents give guidance on how to harmonise quality standards and are recommended for implementation at an operational level within each CTU [24].

Periodic reviews of these management systems are imperative to assure the effectiveness of the applied quality measures in assuring GCP compliance. The first independent evaluation of all CTUs, initiated by the SCTO in cooperation with Swissmedic, was completed in 2011. In the final inspection report, Swissmedic rates three out of six CTUs as "well-structured and organised" (based on the internationally recognised assessment criteria by the European Medicines Agency [EMA]), and reports 34 findings overall (no critical, 4 major, 30 minor) [25]. By the end of 2012, the CTUS had completed all required improvement measures and thereby reached an important milestone with regard to the harmonisation and continuous quality improvement within the network.

Whilst quality can be assured at an operational level through compliance with GCP criteria, defining and measuring quality in the clinical research setting can be difficult. The most important variable involved is the ever-unpredictable human and advancements, such as electronic data capture and internationalisation, are constantly altering the clinical trials landscape [26]. By forming a unique decentralised network of Swissmedic-audited competence centres for the conduct of clinical trials across all medical disciplines, the CTUs may substantially contribute to the quality and safety of clinical research in Switzerland overall. There is, however, an urgent need for the systematic assessment of the actual impact of CTUs on clinical research quality.

## Future direction

In spite of these investments into clinical research infrastructure, the number of clinical drug trials reported to Swissmedic decreased from 318 in 2009 to 237 in 2012 [7]. In a 2013 report [28], the Swiss Federal Council identified underlying causes for the reduction of studies performed in Switzerland, and other factors critically influencing clinical research in Switzerland. Global factors include general shifts of trials into countries with facilitated recruitment, shifts into "new" markets, and the increasing number of multinational (multicentre) studies. National factors were divided into three categories; a complex regulatory landscape (including hurdles for registration and approval, conduct, inter-regional heterogeneities); the aspect of patient-orientation, including difficulties with recruitment; as well as a general lack of resources (financial, qualified personnel). In all of these three areas significant changes have been initiated that are expected to have an important impact on the Swiss research environment. As outlined in the following paragraphs, CTUs will play a major role in shaping these different areas.

### Regulatory landscape

The regulatory framework for clinical research in Switzerland has considerably changed. In January 2014, the enactment of the new law on research with human beings (Human Research Act, HRA) and its ordinances was conceived as a major step forward in creating favourable conditions for research in Switzerland. The purpose of this Act is not only to protect the dignity, privacy and health of human beings involved in research, but it is also designed to reduce regulatory and administrative hurdles, help to ensure the quality of research and create transparency [29]. Clear improvements for research conduct have been achieved by introducing the parallel submission process to ethics committees and competent authorities. Additionally, the new lead ethics committee process should reduce approval time for new study protocols and alleviate inter-regional differences between ethics committees. Furthermore, the newly introduced risk categorisation allows the differentiation of low and high risk trials, with significant facilitations for the conduct of low risk studies. As the low-risk situation often applies to academic clinical research it is expected to improve significantly the research environment at academic institutions. Furthermore, the introduction of a national study registry is a major step forward in creating transparency and should increase the trust of the different stakeholders in clinical research.

It is, however, too early to judge to what extent these promises will hold true. A meaningful analysis of approval times and the impact of risk categorisation on the academic research landscape will be possible only in some years. Meanwhile, CTUs are mainly responsible for the implementation of the new law at the local institutions and are in close contact with the newly created scientific secretariats at the ethics committees. Furthermore, CTUs are involved in almost all of the national projects evaluating the new law initiated by the Federal Office of Public Health. Therefore, it is expected that they will have an important impact on the operationalisation of the new law and are able to shape future modifications.

### Patient recruitment and consent

Recruitment of adequate patient numbers in a clinical research project is one of the major hurdles in the successful completion of a trial. Although the reasons for poor recruitment are multifarious, some factors can be directly addressed by the CTUs. Very importantly, CTUs should invest more resources in consulting investigators about feasibility aspects and the consideration of patient involvement in their trials. Many problems in patient recruitment, such as incompatible inclusion and exclusion criteria, competing studies at the same institution, lack of personnel and finan-

cial resources can be anticipated with thorough planning. Secondly, CTUs play a leading role in the local implementation of processes and structures that ensure consent of patients to the reuse of their data and specimens for research purposes according to the new law. Successful implementation of such a process will be crucial for the set-up of biobanking projects and the conduct of retrospective studies. Furthermore, through the strengthening of collaboration between the different CTUs, they should also play an important role in assuring efficient recruitment for multicentre projects. The potential of a national CTU network with respect to patient recruitment has not been fully exploited so far.

**Funding model of clinical research**

Excellent and independent clinical research requires adequate resources. Most of the competitive research funding in Switzerland is allocated on a per-project basis and does not account for the availability of research infrastructures, which is a prerequisite for planning and conduct of a specific trial. With the exception of cancer research, which has its own research infrastructure (Swiss Academy for Clinical Cancer Research, SAKK), infrastructures for clinical research in other indications is funded by the home institutions, i.e. the universities or the university hospitals.

This imbalance has been recognised by the Swiss State Secretariat for Education, Research and Innovation (SERI), which is willing to fund the establishment of a nationwide infrastructure for clinical research as part of the Swiss Roadmap for Research Infrastructures 2017–2020. This is a unique chance for the CTU network to further develop CTUs into permanently existing and easily accessible infrastructures, which collaborate on a national level in the different service areas. The creation of national service pools will avoid the costly maintenance of parallel structures, make best use of complementary expertise present at the different CTUs and, finally, allow efficient support of multicentre projects as a prerequisite for high quality clinical research. So far, a first concept for the build-up of such national research infrastructures has been submitted to SERI. The approval and long-term funding of such a project will be crucial to reshape the clinical research landscape in Switzerland and to reach sustainable clinical research quality.

## Closing remarks

Taken together, the national and local investments in the build-up of CTUs has been a major step forward in assuring a more favourable environment for academic clinical research in Switzerland. Data from the CTU Basel show the substantial contribution to the planning and conduct of both academic and industry-sponsored studies, and the overall quality of research. The continuous expansion of the different CTUs over the last 7 years and the growing request for support in the different areas of study planning and conduct show that CTUs respond to the needs of clinical scientists. Furthermore, together with the SCTO, the CTU network was successful in creating national awareness for challenges and hurdles that are still counterproductive to excellence in clinical research. More coordination of the different CTUs combined with a national funding model will be critical success factors to overcome these hurdles and to position clinical research at the forefront in Switzerland and in Europe.

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