REGULATORY
AFFAIRS
PLATFORM

REGULATORY AFFAIRS WATCH

TEST ISSUE 0, 20 DECEMBER 2018

Unique, credible, and quarterly updates on regulatory topics relating to clinical research

IN THIS ISSUE

WELCOME!

The Regulatory Affairs (RA) Platform of the SCTO is pleased to present its test issue of the ***Regulatory Affairs Watch*.**

First, we would like to introduce the RA Platform. We are one of the eight SCTO Platforms created in 2017, together with: Auditing, Data Management, Education, Monitoring, Project Management, Safety, and Statistics and Methodology. As a centre of excellence set up to improve the quality of clinical research in Switzerland, the RA Platform aims to

- increase and accelerate harmonisation and cooperation nationwide, through the exchange and dissemination of information regarding regulatory topics
- share aligned interpretation of the laws, regulations, practical recommendations, relevant tools, and resources
- become a national point of contact for authorities and any stakeholder for specific regulatory topics linked to clinical research
- ensure greater exchange and alignment with Europe and beyond

Members of the RA Platform are regulatory experts from the different CTUs (Lausanne as coordinator of the platform, and Basel, Bern, Geneva, St.Gallen, Ticino, and Zurich) and the SAKK (Swiss Group for Clinical Cancer Research). There is also a SCTO representative (liaison officer) and, at times, external experts may be invited to join the platform for specific topics.

Our platform members, from left to right:
Jörg Willers, Pascale Wenger, Erika Küttel, Laure Vallotton, Christina Huf, Sonia Carboni, Elke Hiendlmeyer, Loane Warpelin, Cristiana Sessa, Séverine Méance. (Excused: Christina Jodlauk, Laura di Petto, Annette Widmann, Francisca Jörger, Peter Durrer, Claudia Arati.)

You can find the full members' list in the **CONTACTS** section below.

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WHAT'S UP?

The Regulatory Affairs Watch
The regulatory framework is a dynamic field that undergoes frequent changes. There are several existing sources of information available on regulatory topics, all differing in their form, language, and target audiences. This array of sources might occasionally lead to different interpretations of the laws and regulatory requirements.

One of the objectives of the RA Platform is to disseminate nationwide a relevant and unique aligned information to all its stakeholders, distilling the best from many sources. To fulfil such an objective, we developed this newsletter. It will deliver **a unique and credible information every quarter on clinical research-related regulatory topics** (existing and in development), concerning Switzerland (or other countries if deemed relevant). This newsletter aims to allow clinical research professionals, trainers, regulators, academics, potential sponsors, patients associations, media, and members of ethics committees to stay up to date and gain a common understanding of laws and regulatory requirements. You will receive this quarterly via email. Issues will also be archived online, with a subscribe option on the RA Platform page on the SCTO website.

The newsletter will include different sections:

- **WHAT'S UP?** All about the RA Platform network and our activities
- A quarterly topic for a "**DEEP DIVE**" summarising an existing law or guideline – or one in development – relevant to clinical research, potentially including conclusions of exchanges with the Swiss authorities
- **HEADLINES AND HAPPENINGS** in Switzerland and abroad (as they may have an impact in Switzerland)
- **TIPS AND TRICKS**, everything you wanted to know, but didn't dare ask…
- **VIEWS AND OPINIONS**, case studies that could illustrate hurdles met and lessons learnt
- **UPCOMING EVENTS**

Please give feedback on this newsletter concept by taking this short survey.
The deadline for feedback is 25 January 2019.

DEEP DIVE

Tackling the regulatory burden in clinical research - Where are we now? Which initiatives?

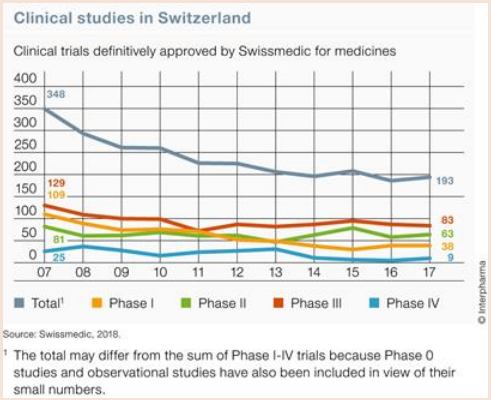
Clinical trials are essential for evaluating the efficacy and safety of interventions. Nonetheless, common barriers limit them by adding complexity that increases labour, impedes speed, and multiplies costs. We propose having a look at initiatives that study these barriers from a regulatory perspective.

Trials waning throughout Europe

Between 2007 and 2011, applications to run clinical trials in Europe experienced a marked decline of 25%.

A similar situation prevailed in Switzerland, as illustrated in the graph on the right. The presently effective EU Clinical Trial Directive 2001/20/EC combined with the shrinking economy may have contributed to this significant decrease.

To explore this trend, Djurisic et al (Trials. 2017, 18:360) performed systematic literature searches and internal European Clinical Research Infrastructure Network (ECRIN) exchanges from 2013 to 2017. This was done within the context of the methodology taskforce of the European Union Framework Programme 7 ECRIN Integrating Activity project.



Identifying key barriers to trials in Europe

Regulatory burdens identified in this study were:

- restrictive privacy laws which impede the flow of health and private information that could help identify patients to be enrolled into clinical trials
- for multicentric studies, which are now more and more necessary, approval by multiple ethics committees with different sets of requirements
- multiple rules and different strategies for data management applied at different research sites or between countries, increasing demand for reporting and storing information combined with inadequate data management systems, which could hamper data quality
- lengthy informed consent forms that include complex legal language, which raises doubts about whether patients are truly informed
- complex safety reporting, including detailed recording of minor events and over-reporting of all serious adverse events to all relevant regulatory authorities, ethics committees, and site investigators.

Accordingly, the European Commission developed a new Clinical Trial Regulation (EU No 536/2014), which aims to simplify procedures and harmonise regulatory requirements across Europe. This new regulation is scheduled to come into force in 2019. The ambition is to ensure that Europe remains an attractive site for clinical research. In a future *Regulatory Affairs Watch* issue, we will come back to this subject, to understand how it may concretely impact on clinical research in Switzerland.

Tackling the top barriers in North America

In Canada, a study about the barriers perceived by physicians in oncology to participation in clinical trials was reported earlier this year (Curr Oncol. 2018 April; 25(2):119-125). Seventy-seven percent of the 207 responders reported having significant time constraints, due to extra paperwork, and suggested streamlining regulatory burden to increase their motivation to participate to clinical research. Results of this study might favour discussions with the authorities to find pragmatic solutions.

In the USA, the American Society of Clinical Oncology and the Association of American Cancer Institutes proposed an interesting initiative to identify and promote solutions to address administrative and regulatory burden in cancer clinical trials (J Clin Oncol. 2016 November; 34(31): 3796-3802). The initiative was overseen by a multidisciplinary working group, with input from the US Food and Drug Administration (FDA). A primary component of the project was a stakeholder survey sent to approximately 1,200 people and a workshop involving leading oncology professionals and policymakers aimed at identifying potential solutions.

The top three burdens identified by respondents were:

- contract negotiations with sponsors and contract research organisations (CROs), and compliance with industry or CRO requirements, in getting clinical trials up and running
- site monitoring visits, management of regulatory documents, and external adverse event and serious adverse event reporting
- sponsor queries of databases and access to records, sponsor-required close-out activities, and long-term follow-up in the area of post-trial completion activities.

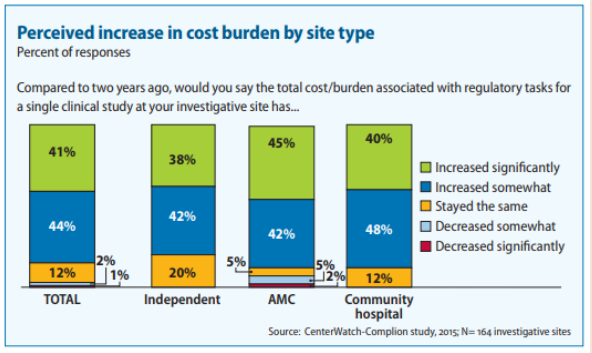
Underestimated perceived burdens, such as staff time

In response to questions about adequacy of research staff, 58% of respondents indicated that they did not have adequate staffing to handle regulatory burden, and 41% reported not having adequate staffing to monitor regulatory compliance. It is interesting to note that the authors of the article claim that institutions, sponsors, and CROs often overestimate regulatory requirements leading to increased complexity in the conduct of clinical research.

Other earlier initiatives in the USA include a CenterWatch survey, sponsored by Complion (a firm creating software for electronically recording clinical trial regulatory documentation), shedding light for the first time on how, and how well, sites manage regulatory compliance. The survey included 164 investigative sites and the results were released in 2015 (CenterWatch Monthly*;* 22(04)).

There was a clear perceived increase in cost or burden associated with regulatory tasks (see graph on the right). An area for improvement for sites, when calculating their study budget, was to not underestimate the staff time required and/or the costs associated with regulatory aspects.

Stein et al (Clin Trans Sci. 2015; 8: 647–654), who surveyed 92 investigators and conducted focus groups, found consistent results with regulatory barriers impeding participant recruitment.



HEADLINES AND HAPPENINGS IN SWITZERLAND

swissethics

Since October 2018, the following new templates have become available:

- 9 October 2018: Template for the notification of serious adverse events (SAE) and device deficiencies to the ethics committees for clinical trials (ClinO) with medical devices.
- 10 October 2018: Template for study protocol (ClinO Chapter 4: Other Clinical Trials).
- 11 November 2018: Template for information to participants to research projects according to HRA/HRO chapter 2 (source: swissethics).

Swissmedic

- 24 October 2018: Federal Council approves Swissmedic's strategic goals for 2019–22.
- 16 November 2018: The modifications following the **Ordinary Revision of the Therapeutic Products Act** (Stage 2) and its right of enforcement will enter into force on 1 January 2019. This will simplify the public's access to medicinal products and improve the conditions for biomedical research.
- **Black ring-binders** need to be used when making submissions to Swissmedic for clinical trial applications of medicinal products between December 2018 and November 2019.
- Authorisation applications and notifications relating to **clinical trials with medical devices** should now, whenever possible, be **submitted to Swissmedic electronically** via the eGovernment Service eMessage. This electronic processing simplifies the submission process.
- 3 December 2018: **Updated procedure for submitting applications according to HMV4 before 1 January 2019.**
  As of 1 December 2018, Swissmedic will accept submissions with the documents updated according to HMV4.
  For eDok submissions, the corresponding cover sheets and templates became available online on 1 November 2018. These new templates are intended for submissions according to HMV4. Submissions that do not yet correspond to HMV4 should continue to use the currently available templates. From 1 January 2019, only eDok submissions using the updated templates will be accepted by Swissmedic. For eCTD submissions, a transitional solution will be provided (source: Swissmedic).

Federal Office of Justice

- 28 September 2018: **Adoption of Schengen Federal Data Protection Act**
  Referendum deadline: 17 January 2019
  Federal Act implementing Directive (EU) 2016/680 on the protection of individuals with regard to the processing of personal data. It is held under the Schengen Agreement and will also approximate the requirements of Regulation (EU) 2016/679. This work is essential for the EU to continue to recognise Switzerland as a third country with a sufficient level of data protection, so that the possibility of exchanging data with it is preserved (source: Federal Office of Justice).

Swiss Academy of Medical Sciences (SAMS)

- 11 December 2018: Ethics. **New guidelines on Assessment on capacity in medical practice**. The presence of capacity is an essential prerequisite for the validity of a patient's consent to medical treatment or care (source: SAMS).

What else?

- November 2018: In order for Switzerland to avoid building a disconnected system in terms of **health data international sharing**, ehealthsuisse is closely following what is happening in Europe. Lately the European commission decided that Switzerland can no longer participate in such projects, because ehealth coordination tools in Europe refer to a directive not currently adopted in Switzerland (source: 52nd *Newsletter ehealthsuisse*, 1 November 2018).

HEADLINES AND HAPPENINGS ABROAD

Europe

- November 2018: Today, in Europe, we are challenged to generate insights and evidence from **real-world clinical data** to support patients, clinicians, payers, regulators, governments, and the pharmaceutical industry in understanding well-being, disease, treatments, outcomes, and new therapeutics and devices. Unfortunately, such data is difficult to use at scale, in a myriad of languages, systems, and structures, with challenging policy restrictions and technology considerations.
  In response to this, the **EHDEN** (European Health Data & Evidence Network) public–private project was set up under the framework of the Innovative Medicines Initiative (2018–2023), co-funded by EFPIA (European Federation of Pharmaceutical Industries and Associations) and the European Commission, with 22 partners including academia, SMEs, patient associations, regulatory authorities, and pharmaceutical companies.
  The mission of EHDEN is to provide a new paradigm for the discovery and analysis of health data in Europe, by building a large-scale, federated network of data sources standardised to a common data model. EHDEN's aspirations are significant, aiming to harmonise 100 million anonymised health records across multiple data sources (source: EFPIA).

- 8 October 2018: **New UK guidance on electronic informed consent.** The National Health Service Health Research Authority (NHS HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA) have issued a joint statement describing the legal and ethical requirements for obtaining informed consent using electronic methods (source: MHRA Inspectorate).

- 14 November 2018: Publication on **Ethics and data protection**. This document has been drafted by a panel of experts at the request of the **European Commission** (DG Research and Innovation) and aims to raise awareness in the scientific community (source: EC Ethics and Data Protection).

USA

- December 2018: **New FDA draft guidance on adaptive trial designs**
  This draft guidance describes the principles for designing, conducting, and reporting the results of adaptive clinical trials. Adaptive designs have the potential to provide a better chance of detecting a true drug effect, while also reducing the number of subjects exposed to ineffective investigational treatments. Because they allow for greater flexibility, they may be more attractive to sponsors, investigators, and trial participants.
  For sponsors in particular, adaptive designs may save both time and money. There may also be ethical benefits, for example from the early termination of trials, when a drug fails due to safety reasons or when it meets pre-specified endpoints early. The deadline for comments on the draft guidance was 30 November 2018. The finalised document will ultimately replace the 2010 draft guidance, 'Adaptive Design Clinical Trials for Drugs and Biologics' (source: Clinical Research. Clinical Quality Assurance Advisor, 2018, 433).

VIEWS AND OPINIONS

Jeffrey Aronson: When I use a word . . . *Regime, regimen, regiment*, and *regulation*

6 November 2018: In the *British Medical Journal*'s Opinion section, Jeffrey Aronson, a clinical pharmacologist working in the Centre for Evidence Based Medicine in Oxford's Nuffield Department of Primary Care Health Sciences, shares some philosophical considerations of the semantic roots of the word "regulation" and its derivatives. Read his article here at the BMJ.

We learn that the IndoEuropean root *REG* meant to move or direct in a straight line, and therefore to lead or rule. This root has numerous ramifications which include all kinds of ruling words, such as *reign*, *regnal*, *regal*, and *regent*, *regime*, *regimen*, *regiment*, and *regulation*.

He also notes that when a law is drafted it will, or should, be good for the time being. In order to allow the law to be amended in response to needs that cannot be anticipated when the original law is enacted, an original Act, whether drafted in broad or specific terms, may contain provisions that allow the enactment of so-called "Delegated Legislation".

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UPCOMING EVENTS

Conferences

- ECCRT Data transparency Conference - Demystifying Clinical Data Transparency: Lessons learnt so far. **Brussels, 12–13 September 2019**

Trainings

- Good clinical practices. **HUG, 16–18 January 2019**
- Good clinical practices. Trainings for clinical investigator/sponsor-investigator, Module 1 to 3. **University Hospital Zurich, January 2019**
- Good clinical practices. **Kantonsspital St.Gallen, 26 February 2019**
- MEGRA (Middle European Organisation for Regulatory Affairs) training: StartUp PV 2019-CH - Module 01: Foundations of Pharmacovigilance for Switzerland. **Brugg, 28 February 2019**
- Clinical investigator/sponsor swissethics training. **CHUV, 11–12 & 18 March 2019**

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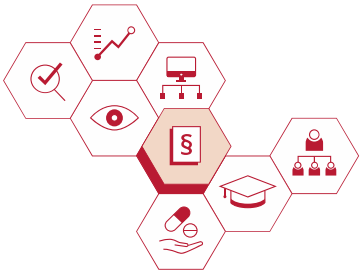

The Swiss Clinical Trial Organisation (SCTO), together with partner organisations, hosts thematic platforms to promote excellence in clinical research in Switzerland. **www.scto.ch**