8th Symposium of the Swiss Clinical Trial Organisation

‘Adding value in clinical research’
1 June 2017, University Hospital Basel

Report of the Symposium
Introduction to the Symposium

On 1 June 2017, the SCTO held its 8th Symposium, a daylong event intended to stimulate reflection, discussion on topical issues in clinical research and to identify potential solutions. As its primary objective, the SCTO aims to position Swiss clinical research attractively and competitively in the international field of clinical research, by emphasising innovation and quality. Accordingly, the 2017 symposium was dedicated to the urgent matter: "Adding value in clinical research: what has been achieved and how do we manage new challenges?"

This topic includes evidence that the majority of resources invested are ultimately wasted. The event was hosted by the University Hospital Basel and attended by 170 representatives from academia, the federal government, the pharmaceutical industry, funding bodies, and the public. Presentations from the day are available at www.scto.ch.

Setting the scene: value vs. waste in clinical research

The topic of waste in biomedical research has come under increasing and critical scrutiny. In particular, in 2014 it was highlighted by a series published in The Lancet, titled: "Research: Increasing Value, Reducing Waste". Waste – estimated to be a staggering 85% of all investment in life sciences research – encompasses unwarranted and poorly designed studies, redundancy, duplication, a lack of transparency, resulting often in inconclusive research, which then may go unpublished or simply be hidden from the public domain.

In his introduction, Prof. Gregor Zünd, President of the SCTO, mentioned that 2017 is also the 10th anniversary of the SCTO’s nationwide clinical trial unit (CTU) network, a milestone for Switzerland regarding value added in clinical research. Celebrating 10 Years of the CTU Network: An SCTO Anniversary Publication, the hot-off-the-press publication marking this landmark and highlighting key achievements and developments among this network – was distributed to participants.

Prof. Zünd framed the key questions to run through the symposium: What are the main sources of wasted resources in clinical research? Which stakeholders are in a position to move towards greater efficiency? Who is already actively reducing waste and how? And what constructive steps can we take to transform waste into value?

A stimulating event ensued, with international researchers and experts from different fields sharing about current and future efforts to increase value, and Swiss experts providing a national view. Brilliant and witty magic tricks were sprinkled through the day by Moderator, physicist, and magician, Mr Thomas Fraps, including genome editing with coloured ropes and a brain-reading device, tuned to aggregate big-data analytics for the mind. Mr Fraps proved that magic acts like placebo. It may not be real, but it works.

The keynote lecture: a snapshot of the poor health of clinical research

In the first session, the keynote lecture by Prof. Rustam Al-Shahi Salman, Professor of Clinical Neurology at the University of Edinburgh (and co-author of the abovementioned 2014 series in The Lancet), addressed value and waste in clinical research, providing examples from his areas
of interest: strokes and "anything that bleeds in the brain". He brought the Swiss a touch of British humour, warning all present against maladies typically afflicting scientists, including *disjunctivitis* (a proclivity to produce large quantities of redundant, trivial, and incoherent works).

Prof. Salman spoke of the importance of The REduce research Waste And Reward Diligence (REWARD) Alliance, a global movement striving to promote ethical and useful research. By assessing the origins of wasteful research, The REWARD Alliance has generated a set of 17 recommendations, some of them simple steps, with related considerations on how to monitor their progress. Similarly, the James Lind Alliance provides a constructive framework and approach, which is bringing researchers back to the drawing board – finding out what patients, carers, and healthcare professionals really want and need. In consultation and via Priority Setting Partnerships (PSPs), 10 research priorities should be established, before research follows. Let us not forget that the public is the recipient and funder of research, if indirectly, and that it has the right to influence and see the fruits of funding.

Troubles plaguing research include studies that are: missing basic and robust methodology and statistics; lacking an up-to-date systematic review; targeting unrealistic numbers of trial participants; showing no evidence of the added value of the given proposal; and trials that are simply registered nowhere. The list goes on. Some researchers provide no context as to how their work will enhance the bank of knowledge in existence. Still other research is poorly conceptualised. It may sit uncomfortably between pointless duplication of theories that are already firmly established (and indeed proven many times over), and proofs that really merit replication for science to advance.

To conclude, Prof. Salman proposed: that Swiss funders and regulators streamline their funding application systems, putting in place fundamental conditions to which applicants must adhere; that more "research on research" and "research in research" be done; that studies demonstrate clear value to patients and the public (according to needs they have actually expressed); and that compliance and diligence in the research and development (R&D) community be duly rewarded, even with modest, but potentially prestigious, monetary prizes.

**Highlighting measures to maximise value, from Switzerland right across Europe**

In the second session, exploring Measures to increase value: Swiss and European networks for research infrastructures, input came from representatives of the University Hospital Basel, the SCTO’s CTU network, the Swiss Biobanking Platform (SBP), and the European Clinical Research Infrastructure Network (ECRIN), respectively.

**Swiss perspectives**

Prof. Christiane Pauli-Magnus, Vice-president of the SCTO and Co-Director of the Department of Clinical Research at University Hospital Basel, examined the hypothesis that CTU network activities correspond to quality. While the CTU network achieves a great deal (including contributing to 260 projects, providing 2,700 services, and running 200+ courses for 3,000+ participants), does this ultimately equate to quality? In a survey of 155 researchers, it was found that the CTU network is considered to be positively influencing the quality of R&D planning throughout its life cycle: from concept and development, to setup, conduct, and completion, and that CTU support does lead to sounder research and higher quality studies.
Prof. Mirjam Christ-Crain, Co-Director of the Department of Clinical Research at University Hospital Basel, provided a positive example of increasing quality in Swiss-based research: a randomised clinical trial run by her team from 2008 onwards, assessing the effect of corticosteroids on community-acquired pneumonia, which was then published in 2015 in *The Lancet*. Yet the trial preparation lacked certain important expertise relating to the concept and development, and to statistical, epidemiological, and regulatory input, since the CTU did not yet offer certain services at that time.

The subsequent version of the trial, approved in June 2017 for funding by the Swiss National Science Foundation (SNSF), will be run next for paediatric patients in Switzerland. But now the CTU has the full range of skills needed and is adhering to key quality indicators stipulated by *The Lancet*: relevance of scientific question, adequacy of design and statistics, efficiency of study, transparency, and publication.

By striving to objectively qualify the impact of clinical research and formulating an academic response within the scientific community, placing ethics, patient safety rights, and patient-relevant outcomes at the forefront, the CTU Basel, in accord with the full CTU network, believes that pioneering for a national perspective will carry international influence.

Dr Christine Currat, Executive Director of the SBP, outlined the future plans of the SBP, efforts that will promote quality in research. The SBP is striving for all biobanks in Switzerland to be harmonised, visible, and accessible, and accordingly is setting up an inventory with an online directory. With the goal of sharing both samples and data kept to high-quality standards, the SBP is sourcing incentives for those biobanks which become part of the catalogue.

Despite their tremendous potential, biobanks are beset with difficulties: many of them keep their records with unsophisticated software, such as Excel spreadsheets, and only 5–10% of the samples stored in freezers are actually accessible. Consequently, the SBP plans to introduce IT support and audits, to promote adherence from biobanks nationwide. The wealth of data in biobanks can only be harvested when researchers can access them.

Against the background of the newsworthy matters of consent, privacy, and ethics, the SBP is drawing up a biobank code of conduct and documenting best practice. Consent is crucial, remembering that samples come from people. The SBP will also raise awareness among the public about the concept of a biobank and its potential value to both researchers and the greater society.

Pan-European perspectives

Dr Christine Kubiak, Operations Director at ECRIN, outlined the primary goal of ECRIN: to support the conduct of multinational clinical trials across Europe, in partnership with national bodies (such as the SCTO and its CTU network). ECRIN, a distributed research infrastructure with its offices based in Paris, offers support to researchers from early stages onwards and believes firmly that such early planning will pay out good
dividends in value. Its scientific board promotes transparency and a commitment both to publishing results and to sharing data, especially individual patient data (IPD), so that they can be used for secondary analysis.

ECRIN encourages researchers to disclose real and relevant questions (including trial hypotheses) so as to find reliable answers via sound trial methodology. Dr Kubiak also noted that ECRIN partners with MiRoR (Methods in Research on Research), which is defined as an emerging new scientific discipline aiming to reduce waste in research and increase research value. It runs a joint doctoral programme, training scientists to apply MiRoR-based rigour to their projects.

Dr Michaela Th. Mayrhofer, Chief Policy Officer of CS ELSI and Senior Project Manager at the Biobanking and BioMolecular resources Research Infrastructure-European Research Infrastructure Consortium (BBMRI-ERIC), described its primary goal as being to provide a pan-European, distributed research infrastructure of biobanks and biomolecular resources to support high-quality biomolecular and medical research. Its directory has about 600 users per month enquiring about biobank databases and how to access them. The SBP is the Swiss node of BBMRI-ERIC.

BBMRI-ERIC, which is has its offices in Austria, is providing those researchers from public and private sectors seeking to use its resources with an improved IT interface, for the storing and searching of databases, and with access to self-evaluation tools that promote quality work.

Furthermore, in order to supply customised assistance, it has launched an ethical, legal, and societal issues (ELSI) helpdesk, advising users and other stakeholders on related issues crucial for biobanking generally (such as informed consent, data protection, and support on ethical questions), as well as advice pertaining to the given research project. Dr Mayrhofer reminded those present that samples come from individuals and are a very precious resource.

Views on increasing value, from funders, policy, and editors

For the third discussion, Measures to increase value: funders, policymakers, and editors, contributions came from the SNSF, University College London, and The Lancet.

Dr Aysim Yilmaz, Head of the Department Biology and Medicine at the SNSF, gave the perspective of national funding. She emphasised that, going forward, the SNSF intends to prioritise data quality, insisting that researchers applying for funding submit a data management plan and commit to making their data open-research, thereby contributing to a national spirit of repository-building. She urged researchers to consult the SNSF evaluation criteria carefully, to follow them thoroughly, and to seek help from the SCTO’s CTU network in the case of clinical research projects. This consulting should happen in the early stages of planning, so as to build the strongest case possible for funding.

Dr Yilmaz said that the SNSF maintains a long-standing commitment to investing in research infrastructures (such as the SCTO and the SBP), in young talent by supporting their careers, as well as in project funding. A notable, specific funding programme is the call for Investigator-Initiated Clinical Trials (IICT), in addition to regular SNSF project funding that remains open for clinical research projects. She noted that only 40% of SNSF-funded clinical research projects succeed, and there is a high rate of discontinued randomised clinical trials, of which a considerable proportion never gets published. Increasingly, the SNSF will be
introducing mechanisms to monitor whether milestones are reached and if not, funding may be stopped.

The SNSF believes research data should be shared as openly as possible and supports open access to publications. Data underlying a publication is expected to be shared according to the FAIR criteria: findable, accessible, interoperable, and useable via non-profit repositories. So that anybody, whether a member of the public, a patient or another researcher, can find it.

Prof. Sandy Oliver, Professor of Public Policy at the University College London (UCL), talked about the interface between research and policy. The way to determine that research is truly useful lies in developing methods to shape its questions, as much as in applying rigorous methods to find the answers. Prof. Oliver provided an example of collective decision-making and consensus development, at the Preterm Birth Programme in the UK and conducted using the James Lind Alliance approach. This project drew input from many parties, via the Internet, surveys, and group interaction.

Collective decision-making means sourcing input across academic disciplines and policy sectors, doing insider research, reflecting, and mapping out how policy and research can inform one another. Such collaboration enables health research funders to find out what matters most to patients and clinicians. And the James Lind Alliance has discovered that what matters most to them is not necessarily drugs, biological treatments, and vaccines. In fact, 74% of them would prefer investment in education and training, service delivery, and other types of assistance, including psychological, physical, and complementary support, exercise and diet.

Dr Joan Marsh, Deputy Editor of The Lancet Psychiatry and member of the REWARD campaign provided an editorial and publishing perspective for all those perishing to be published. Drawing on the origins of the journal, she noted that its name, lancet, means both "an arched window to let in light and a sharp surgical instrument to cut out the dross (waste)".

Dr Marsh spoke about the submission process and quality criteria the journal has established, in seeking to publish the finest research. In its "Research in context panel" for each submission, authors must supply a summary of literature searched to provide a convincing case for the added value of the research and the implications for practice or policy and future research of their study, combined with existing evidence. All trials must be registered – a practice that other significant medical journals are increasingly expecting – and must comply with CONSORT 2010 guidelines.

The Lancet cannot yet demand that all trial data be fully accessible, such as when patients' details are not fully anonymised, making this consideration logistically still very challenging. Only after a submission has passed a study protocol check, will The Lancet have it peer reviewed. The editor then puts the manuscript through statistical review, clinical review, and peer review by subject experts.

As for research that draws disappointing results (referred to as "negative studies"), Dr Marsh said that failed studies can be valuable, too. By making the findings known, they can inform meta-analyses and provide the "last word", and in so doing, prevent futile and wasteful repetition by others.

Debating big data and personalised medicine

An Oxford-style debate followed, to explore one of the hottest topics in medicine today. The statement put forward was: "This house believes that big data will deliver a revolution in personalised health care." Big data,
sensors, new technology, and smart devices all promise a radical change in medicine, with more accurate disease diagnosis and better outcomes for patients. But is this prediction all hype? Do big numbers necessarily equate to greater, more meaningful, and less wasteful results?

Debating in favour of the statement were: Prof. Alexandre Reymond, Director of the Centre for Integrative Genomics (CIG) at the University of Lausanne and Prof. Effy Vayena, SNSF Professor of Health Policy and Division Head of Health of Ethics and Policy Lab at the University of Zurich. Opposing it were: Dr Stephen Senn, Head of the Competence Center for Methodology and Statistics (CCMS) at the Luxembourg Institute of Health, and Prof. Gerd Antes, Co-Director of Cochrane Germany. The debate was chaired by Dr Margrit Leuthold, Manager of Medical Research at ETH Zurich.

After some captivating and entertaining presentations, the vote was swayed dramatically. While the pre-debate vote was roughly half "for" and half "against", after provocative input and a revote, those disagreeing with the statement shot up to 70%.

**Conclusion**

Prof. Christiane Pauli-Magnus drew this engaging and enriching day to a close. Despite the long path ahead to dismantling some of the most prevalent wasteful practices in clinical research, Prof. Pauli-Magnus pointed out how many practical, relatively easy, constructive, and meaningful strategies do exist to start this process.

As a small country, Switzerland has the power to set an example for other, much larger ones, and to contribute to making clinical research lean and healthy, internationally.

The SCTO wishes to thank the Swiss National Science Foundation and the State Secretariat for Education, Research and Innovation for its support, including this event.
About the SCTO

New and better therapies through research

The Swiss Clinical Trial Organisation (SCTO) is the central cooperation platform for patient-oriented clinical research in Switzerland. Its primary objective is to attractively and competitively position Swiss clinical research in the international competition, with respect to innovation and quality.

The SCTO intends to achieve this mandate by:

- Promoting a high-quality and nationally harmonised study culture – including the continuing education necessary for this purpose
- Supporting the formation of a national network
- Facilitating the integration of national clinical research into international networks
- Promoting the transfer of knowledge between basic research and therapeutic applications
- Building bridges between academia, industry, and public authorities, as well as trade organisations and professional associations
- Advocating favourable conditions in the field of clinical research in general

For further information see [www.scto.ch](http://www.scto.ch)

The SCTO is a joint initiative of the Swiss National Science Foundation (SNSF) and the Swiss Academy of Medical Sciences (SAMS). Since 1 January 2013, the SCTO has been acting as an independent organisation.

Save the date

In 2018, the SCTO Symposium will be replaced by the 2nd DACH Symposium, the joint three-nation congress on clinical trials. The event will be held on 11 and 12 June 2018 in Zurich.