UCR
Uppsala Clinical Research Center

Kliniska Studier Sverige
Forum Uppsala-Örebro

RAPPORT 4

NORDIC CONFERENCE ON PRAGMATIC CLINICAL STUDIES

12–13 DECEMBER 2017, UKK, UPPSALA, SWEDEN

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NORDIC TRIAL ALLIANCE

THANK YOU FOR YOUR PARTICIPATION IN THE 1ST NORDIC CONFERENCE ON PRAGMATIC CLINICAL STUDIES

We were pleased that the *1st Nordic Conference on Pragmatic Clinical Studies,* arranged in Uppsala, Sweden on December 12–13 last year, attracted so much attention and interest!

Around 170 attendees from academia, healthcare sector, industry, SMEs, and government attended the event, a collaboration between Uppsala Clinical Research Center (UCR) and Forum Uppsala–Örebro (FUÖ) with financial support from the Nordic Trial Alliance.

We trust that this *1st Nordic Conference on Pragmatic Clinical Studies* provided good opportunities for networking and interesting discussions in a relaxed atmosphere in a snowy and wintery Uppsala. The conference feedback indicated that the speakers and their topics were highly appreciated, and that there is an interest to further evaluate opportunities and challenges with pragmatic clinical studies. All presentations and discussions are summarised in this report.

We, the steering committee, have found it rewarding to provide a platform to discuss pragmatic clinical studies, and are proud to see the work being performed at UCR and FUÖ contributing to the advancement of the field.

Please visit the conference website (npcs.se) for information on follow-up activities.

We hope to see you soon again.

Jonas Oldgren
Executive Director UCR

Patric Amcoff
Director FUÖ

Raf Lemmens
Director UCR

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NORDIC CONFERENCE ON PRAGMATIC CLINICAL STUDIES

12–13 December 2017, Uppsala Konsert & Kongress (UKK), Uppsala, Sweden

Summary

Evidence-based healthcare has evolved greatly in recent decades, but the evidence gap is still huge in several areas of medicine. At a time when costs for prospective clinical trials are skyrocketing, clinical researchers worldwide are looking for faster, better, and more cost-effective alternatives to clinical trials to generate new scientific evidence. Pragmatic randomised clinical studies focusing on the effectiveness of treatments in routine healthcare can, when properly designed and conducted, provide solid evidence and guide treatment guidelines in a quicker, broader and more effective way than conventional randomised trials.

The first Nordic Conference on Pragmatic Clinical Studies brought together researchers, healthcare professionals, regulatory agencies, patient representatives, research organisations, and medtech and pharmaceutical companies from ten countries for two days of presentations and discussions around opportunities and challenges with pragmatic clinical trials.

After the amazing digital development of registries and health records during recent years, the current challenges for pragmatic studies are curating and collaborating around data rather than generating data. Infrastructures now have to be leveraged and combined rather than created. The important clinical questions now have to be asked, because the answers are already there to retrieve.

Creative and promising examples of ongoing and completed pragmatic trials, often based on healthcare registries, were presented. The concept of registry-based randomised clinical trials (R-RCT) is maturing and Swedish national guidelines for R-RCT will soon be available.

Challenges and hurdles remain, legislative as well as ethical and practical. The new EU regulation on clinical trials introduces low intervention clinical trials, but they need to be further defined. Questions around the use of electronic patient consent need to be fully resolved.

The conference schedule and setting encouraged interaction between speakers and audience and induced fruitful discussions among participants with different backgrounds. Many attendees advocated the unique opportunity, and responsibility, of the Nordic countries to leverage the countries' respective strengths and take the international lead in evolving pragmatic clinical studies.

The Nordic Conference on Pragmatic Clinical Studies was organised by Forum Uppsala–Örebro, part of Clinical Studies Sweden, and Uppsala Clinical Research Center (UCR). The conference was funded by the Nordic Trial Alliance.

Session I: Pragmatic clinical studies in the context of healthcare and registries

Organisers **Patric Amcoff,** Director of Forum Uppsala–Örebro, and **Jonas Oldgren,** Executive Director of Uppsala Clinical Research Center (UCR), greeted the attendees and opened the conference with an attempt to define pragmatic clinical studies (Table 1). Briefly, traditional clinical trials are usually designed to test causal research hypotheses and to measure efficacy: the benefit of a certain treatment under ideal conditions. Pragmatic trials, on the other hand, are designed to help choose between care options and to measure effectiveness: the benefit of a treatment in routine clinical practice. There is, however, no adopted regulatory definition of pragmatic clinical studies.

Jonas Oldgren stated that most randomised clinical trials performed today are too small and too expensive to be able to answer the clinically important questions: "We need trials of larger size and higher quality. We need faster and better-designed trials. We need more cost-effective trials. And we need them now for the benefit of the patients."

Keynote lecture: Pragmatic clinical studies in the context of healthcare and registries

Robert Califf, Vice Chancellor for Health Data Science, Duke University, NC, US; Adviser at Verily, South San Francisco, CA, US; Former Commissioner of the US Food and Drug Administration (FDA).

"There could not be a more exciting time to talk about pragmatic clinical trials," said Robert Califf. "This marriage of knowledge and technology is now at a point where it is about to take off."

Robert Califf believed that we are heading towards an information revolution, and that the challenges are now mainly cultural and social rather than technological. He stated that the current process to generate evidence, by conventional randomised clinical trials (RCT), is inadequate and too expensive: "In cardiology, less than fifteen per cent of guideline recommendations are supported by high-quality evidence, and the situation is worse in other specialties. This is now in our power to fix with technology."

"An improved organisation, a learning healthcare system, is now developing rapidly

Table 1. Differences between traditional and pragmatic clinical studies.

	Traditional clinical trials	Pragmatic clinical studies
Research question	Is the treatment efficacious under ideal circumstances?	Is the treatment effective in clinical reality?
Aim	Test a biological or mechanistic hypothesis	Assess a question that matters to patients and decision makers
Patient selection	Narrow	Broad, representative
Endpoints	Surrogate, mechanistic	Clinically important
Goal	Deeper scientific understanding	Guide treatment choices

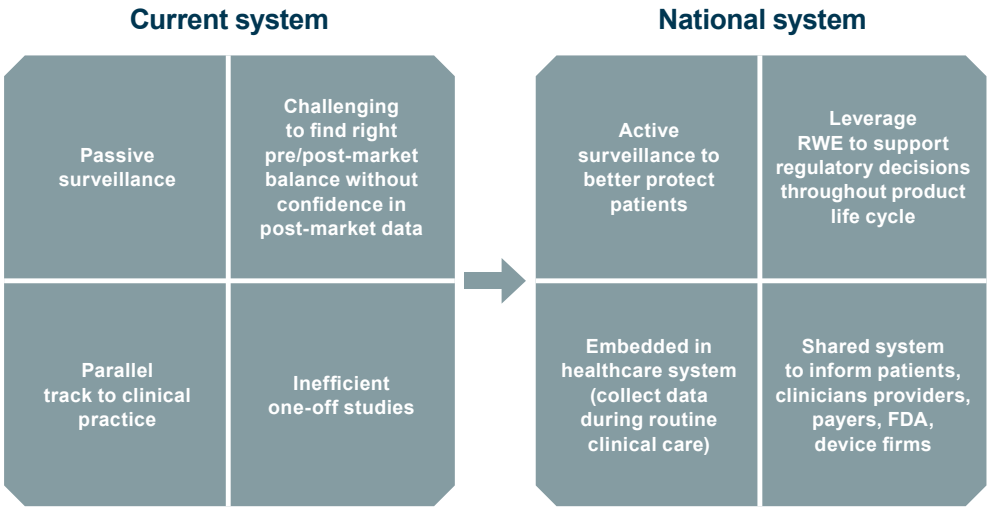

Figure 1. Outline of US national system paradigm shift. Adapted from Prof Califf's presentation.

and following the same principles as companies who are winning in the global competition," said Robert Califf. "It seemed like a distant dream ten years ago, but now the vast majority of the over 300 million Americans have electronic health records. So every time we touch the healthcare system there is a digital record made of it."

The digital information collected across the country can be combined, analysed, and the results can be fed back as decision support to improve healthcare practice. Robert Califf said that it is early days and the systems are far from perfect, but previously independent sites are now coming together to form larger, integrated health systems.

In addition, several public-private partnerships are developing national systems that can generate reliable evidence quickly. Two examples are the FDA Sentinel[1] and the NEST[2] networks for surveillance and trials of drugs and medical devices, respectively. According to Robert Califf, these networks should be well suited for pragmatic clinical trials.

Another important network is PCORnet[3] for post-market studies, including comparative effectiveness studies. In PCORnet, patients are directly involved in defining the key questions, in designing, and in interpreting the studies. PCORnet currently joins 122 million patients with clinicians, health systems, and coordinating centres.

Robert Califf described the organisational paradigm shift that the FDA has in mind for the near future (Figure 1): a shift from the current passive system with one isolated RCT after the other to a network system with constant surveillance and clinical trials embedded in routine clinical care.

Another large effort is the NIH Collaboratory system[4] that investigates if clinical trials can be conducted in a better, faster, and cheaper way. In Collaboratory, health systems have to be willing to share and combine their data and to proactively contact patients that are eligible for clinical studies. One ongoing Collaboratory study is the Suicide Prevention Outreach Trial[5], a pragmatic trial comparing two outreach interven-

1. FDA Sentinel Initiative https://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
2. FDA National Evaluation System for Health Technology (NEST) https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm301912.htm
3. National Patient-Centered Clinical Research Network (PCORnet) http://www.pcornet.org/
4. NIH Collaboratory http://www.rethinkingclinicaltrials.org/
5. Suicide Prevention Outreach Trial http://www.rethinkingclinicaltrials.org/uh3-project-suicide-prevention-outreach-trial-spot/ ClinicalTrials.gov NCT02326883

tions to reduce long-term risk of suicide attempt. Patients identified as of high risk are contacted, and randomisation to outreach method is made at the doctor level. The study has enrolled 12,000 people, and would not have been possible to perform without the wide-scale availability of data.

Robert Califf further stated that the goal should be to not only do studies that are valid, in the sense that they meet the criteria of being reproducible, but also to do studies that are generalisable: "The typical RCT does not meet those criteria. You need constant information on the entire population and a sample that represents that population. Randomised clinical trials have generally involved younger and less sick patients."

Robert Califf splits his time between Duke University and Verily, a Silicon Valley company within the Alphabet family. He therefore also gave the audience a 'glimpse of the future':

- The Baseline study[6] at the Duke and Stanford Universities is a collaboration with Google on mapping human health. Smart watches, mobile apps, and sleep monitors are used to record patient health information.
- Verily works on making health information universally accessible and useful. One in 20 Google searches are health-related, and Verily joins forces with Google to provide curated and helpful health information.

Robert Califf concluded his lecture by reinforcing what we need to do to handle the new digital opportunities:

1. Become stewards of data. Make sure we create better and better information.
2. Work on sharing. The old academic way of hoarding information has to go.
3. Learn continuously from the data. In business, the standard way of answering questions is A/B testing. An A/B test is simply a pragmatic randomised trial. We have to do that more in healthcare.

Finally, Rob Califf stated that we have to learn how to learn together: "I hope, as we accrue much more powerful aggregate information, using the principles of data sharing and taking advantage of the registries, we can accrue medical knowledge faster and learn how to better treat patients."

Pragmatic clinical trials – for label inclusion?

Elisabeth Björk, Vice President Cardiovascular and Metabolic Diseases, Head of Late Stage Development, AstraZeneca, Gothenburg, Sweden

After 100 years of research, AstraZeneca has extensive experience in conducting clinical trials and still holds a strong portfolio in cardiovascular and metabolic diseases. Elisabeth Björk said that with over 70,000 patients involved in clinical trials worldwide, the company is very interested in alternative ways to perform trials. One of the reasons to look deeper into pragmatic clinical trials, which she defined as registry-based randomised clinical trials (R-RCT)[7], is that a very small proportion of actual patients meet the eligibility criteria for conventional clinical trials.

For studies within the current label and for retrospective studies, Elisabeth Björk thought that observational studies are still very useful. She considered indication/label-changing trials to be the next logical step in the R-RCT journey, but they do

6. Project Baseline https://www.projectbaseline.com/ ClinicalTrials.gov NCT03154346
7. Registry-based Randomised Clinical Trials (R-RCT) http://www.ucr.uu.se/en/services/r-rct

present new challenges. Elisabeth Björk listed the requirements for a successful label-changing registry trial:

- Patient population with relevant information contained in registries.
- Drug with a well-known and acceptable safety profile.
- Assumed effect on endpoint that would be easily accessible in registries and easy to standardise.
- Effect size reasonably big.
- Way to collect safety data.

"We also need to collect consent in a way that enables physicians to screen for suitable patients," said Elisabeth Björk.

Elisabeth Björk further stated that regulatory agencies are giving a clear message that they want specific proposals to consider and that companies need to take the first steps and collaborate towards making pragmatic trials a reality. She identified the next steps as:

- Improve and harmonise data collection from for example electronic health records.
- Clarify current and new privacy legislation implications.
- Work with regulators to allow a novel framework for reporting adverse events.

Finally, Elisabeth Björk encouraged new ideas: "Spotify was not developed by music lovers. Uber was not developed by taxi drivers. Patients can be the winners if health-care, industry, and academia can collaborate. We in the Nordic region has an absolute unique opportunity to accomplish this."

Patient preferences in the benefit-risk assessments during the drug life cycle (PREFER)

Mats G Hansson, Coordinator, PREFER, Uppsala, Sweden

The PREFER[8] project aims to strengthen patient-centric decision-making throughout the life cycle of medicinal products, including medical devices. PREFER coordinator Mats Hansson said that there is a lack of understanding of how patient perspectives on benefits and risks can best inform decision-making. "How is a [clinical] study relevant for patients? And for what patients?" he asked.

The goal of PREFER is to establish evidence-based recommendations on how and when to include patient preferences on benefits and risks of medical projects and how patient preferences can support decision-making. PREFER is a public-private partnership including academic research organisations, biopharmaceutical companies, patient organisations, health technology assessment bodies, and small and medium-sized companies. The project is coordinated from Uppsala University.

The first step is to identify reliable methods to assess patient preferences. "We need methods with scientific rigour to know that a patient is well informed when he or she accepts a treatment," said Mats Hansson. "We then need to study what matters to patients. How much does it matter? And what matters most?"

The next step for PREFER will be to run clinical case studies in three disease areas where patients and clinical research partners already provide expertise: cancer, rheumatoid arthritis, and neuromuscular disorders. Industry partners will conduct patient preference studies in additional disease areas.

8. PREFER http://www.imi-prefer.eu/

Mats Hansson explained that a complicating factor in conducting and interpreting the results from patient preference studies is the notable heterogeneity among patients. For example, patients with diseases at different stages will accept different levels of adverse events. "How should a doctor incorporate patient preferences based on a large group when seeing an individual patient?" Mats Hansson asked.

Finally, PREFER will draft and have stakeholders evaluate recommendations on how and when to include patient preferences. The project expects to present their final recommendations in the autumn of 2021.

How can we conduct trials in a smarter way?

Stefan James, Scientific Director, UCR, Uppsala, Sweden

Stefan James talked about evidence-based healthcare development and the importance of implementing new knowledge in treatment guidelines and in the design of further, evidence-based research studies. He explained that the gap between evidence and need for evidence in medicine is enormous. But while costs associated with clinical trials increase, the technical development continues. "A new path making use of clinical registries and digitalised health records is indicated," he said. "Pragmatic trials can facilitate better, faster, easier, and more cost-effective clinical research."

Pragmatic studies are usually described as easy, but Stefan James cautioned that they still need thorough planning to be successful. He used the analogy of decorating a Christmas tree:

- The usual clinical trial, after regulatory/FDA/academic interactions, is like an over-decorated tree: beautiful, but expensive and cumbersome.
- The poorly planned pragmatic trial is simple, inexpensive, but inappropriate, like a sad and poorly decorated tree.
- The good enough, adequately decorated Christmas tree equals a well-planned and well-conducted pragmatic trial.

Stefan James then described how prospective registry-based randomised clinical trials (R-RCT)[9] have been developed at UCR in a stepwise manner:

1. Medical device

The TASTE[10] study assessed the clinical benefit of thrombus aspiration during percutaneous coronary intervention after a myocardial infarction. "Thrombus aspiration seemed like a good thing to do," said Stefan James. "We could see the thrombus and we had the tools to aspirate it. But was it really helping the patients?"

TASTE was designed with patient inclusion and randomisation directly incorporated in the SWEDEHEART[11] national quality registry, few inclusion criteria, an electronic consent form and registry follow-up only. Sixty per cent of all eligible patients, 7,244 patients in total, were enrolled in less than three years. The results showed that thrombus aspiration was not beneficial, and international treatment guidelines were revised accordingly. "But the methodology got even more attention than the results," recalls Stefan James. "The study was cheaper than a conventional trial, but more importantly, it was simple and easy for patients and clinics."

9. Registry-based Randomised Clinical Trials (R-RCT) http://www.ucr.uu.se/en/services/r-rct
10. TASTE ClinicalTrials.gov NCT01093404
11. SWEDEHEART National Quality Registry http://www.ucr.uu.se/swedeheart/

> *"Here in the Nordic countries you are doing ground-breaking work in pragmatic studies that are not being done anywhere else in the world. As we become more integrated in the United States across healthcare systems and across common data infrastructures I think we can try to simulate what you are doing here."*
>
> Matthew Roe,
> Professor of Medicine, Duke Clinical Research Institute, NC, US

2. Pharmaceutical agent – oxygen

The DETO$_2$X-AMI[12] trial studied if oxygen therapy was useful compared to breathing ambient air in patients with suspected myocardial infarction and blood oxygen saturation of at least 90%. Patients were enrolled already in the ambulance, and the primary endpoint was one-year total mortality. The results showed no benefit of oxygen therapy, leading to a change in international treatment guidelines.

3. Compare two pharmaceutical agents

The VALIDATE-SWEDEHEART[13] trial compared two pharmaceutical agents, bivalirudin and heparin, given at a single timepoint during treatment of myocardial infarction. The cheaper heparin was shown to be just as effective as bivalirudin. VALIDATE used more complex endpoints than previous R-RCTs as well as conventional clinical events adjudication. A follow-up comparison of conventional and registry-based adjudication is planned.

4. Compare long-term treatment options

UCR is now moving into comparing long-term pharmacological treatment in heart failure, spironolactone vs standard of care, in the ongoing SPIRRIT-HFpEF[14] study. SPIRRIT is event-driven and includes extra safety reporting. The study will be conducted in Sweden and in the United States. The US part of SPIRRIT is supported by a grant from the National Insitute of Health.

Development of the R-RCT concept at UCR continues, and Stefan James concluded by emphasizing that prospective randomised studies are at the core of evidence generation in medicine.

12. DETO2X-AMI http://www.deto2x.se/english/ ClinicalTrials.gov NCT01787110
13. VALIDATE-SWEDEHEART ClinicalTrials.gov NCT02311231
14. SPIRRIT-HFpEF http://www.ucr.uu.se/rikssvikt/rrct/spirrit-hfpef/om-spirrit-hfpef ClinicalTrials.gov NCT02901184

Panel discussion

Elisabeth Björk, Vice President Cardiovascular and Metabolic Diseases, Head of Late Stage Development, AstraZeneca, Gothenburg, Sweden
Mats G Hansson, Coordinator, PREFER, Uppsala, Sweden
Stefan James, Scientific Director, UCR, Uppsala, Sweden

Comments on the efforts needed to gather a large number of clinics and doctors to a study (SJ)

- Stable funding of the participating clinical registry is important.
- Evidence is important. Patients need to be able to rely on doctors' evidence, not their beliefs.
- May have been easier to make cardiologists come together as they are more used to evidence-based medicine. We are facing this challenge now as we are moving into several other disease areas and clinical registries.

Most prior studies have been done in the acute setting where it is relatively easy to find patients and get consent. How do we move to a more chronic setting?
SJ: We need to go stepwise and we need to make the systems easy to use. We need to discuss at meetings, in clinics, and in society as a whole.

Who should decide what trials to perform and how to prioritise them?
MGH: I would like to see more patient input.
EB: At the moment, a stepwise approach of gradually more complex pragmatic studies is wise.
SJ: One step forward would be cross-over designs and randomisation clusters that eliminate the need to approach each patient. Patients can then be included in many trials.

Session II: Regulatory challenges to pragmatic clinical studies in the Nordic countries

Opportunities and challenges to pragmatic clinical studies from a regulatory perspective

Rolf Gedeborg, Scientific Director for Epidemiology and Pharmacovigilance, Swedish Medical Products Agency (MPA), Uppsala, Sweden. Replacing Catarina Andersson Forsman, Director General of the Swedish MPA

Rolf Gedeborg focused on the new opportunities for clinical trials contained in the new clinical trial regulation (EU 536/2014)[15, 16, 17], currently expected to come into force during 2019.

Firstly, it will be easier to conduct clinical trials in emergency situations where the patient is unconscious and informed consent cannot be obtained. This is provided that (i) the clinical trial relates to the medical condition because of which it is not possible to obtain informed consent, (ii) any previously expressed objection by the patient should be respected, and (iii) informed consent should be sought as soon as possible.

Secondly, the new regulation will introduce the concept of low intervention clinical trials. Low intervention trials study already authorised medicinal products that are used either in accordance with marketing authorisation terms or in an evidence-based manner supported by published scientific evidence. In addition, the diagnostic or monitoring procedures added by the study cannot pose more than minimal extra risk or burden compared to normal clinical practice. These trials are subject to the same application procedure as any other clinical trial but should be subject to less stringent rules in terms of for example monitoring requirements and safety reporting.

Rolf Gedeborg also presented the European Medicines Agency (EMA) policy on publication of clinical data for medicinal products (EMA policy 0070)[18], by which anonymised clinical data submitted by pharmaceutical companies in applications under the centralised procedure are published, starting from October 2016. EMA now collaborates with others to find the most appropriate way to make also individual patient data available. “There is always a trade-off between privacy and the utility of data,” explained Rolf Gedeborg.

Pragmatic clinical trials from the perspective of a cancer patient

Bettina Ryll, Chair, European Society for Medical Oncology (ESMO) Patient Advocates Working Group, Uppsala, Sweden

Bettina Ryll started by opposing why we always talk about ‘challenges’ of new treatments. “This assumes that what we are currently doing is perfect and right,” she said.

Bettina Ryll’s husband was diagnosed with advanced melanoma in 2011. He died less

15. European Commission website https://ec.europa.eu/health/human-use/clinical-trials/regulation_en
16. European Medicines Agency (EMA) website http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp&mid=WC-0b01ac05808768df
17. EU Legislation https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
18. EMA policy on publication of clinical data for medicinal products (EMA policy 0070) http://www.ema.europa.eu/ema/?curl=pages/special_topics/general/general_content_000555.jsp

than one year later. At that time, two-year survival with melanoma was only 15%, and the best chance to survive was to get into clinical trials with new immune- or targeted therapies – therapies that four years later would have increased the two-year survival to 64%. “Entering trials was the only way to receive treatment, but the trials were small and inclusion criteria were very strict,” recalls Bettina Ryll. “Early studies also had a large focus on safety. I would have liked the same attention paid to effectiveness.”

But even after market approval of the new therapies, patient access remained poor. In a situation with high unmet medical needs, the new drugs came at a very high cost. Consequently, health technology assessments restricted access to only those patient populations that had been included in the pre-approval clinical trials. “The original trials had been small and only included the healthiest stage four patients, for example excluding brain metastases,” explained Bettina Ryll. “But eighty per cent of the patients have brain metastases at death and those metastases are the main killer.”

Bettina Ryll would therefore welcome further, more pragmatic, clinical trials to assess the clinical relevance and cost-effectiveness of the treatments in larger and more diverse patient populations.

To complicate matters further, immune therapies are inherently different from traditional drugs regarding dose-response relationships and interindividual differences in response and adverse effects. “New drugs with different modes of action also need different analyses,” said Bettina Ryll, “from trial design over response criteria to evaluation of efficacy.”

Finally, Bettina Ryll emphasised the great risk of *not* taking risks when it comes to life-threatening diseases: “Patients in desperate situations, like advanced melanoma, need early access to innovative therapies and fast and systematic learning,” she stated. “But there is also no such thing as ‘the’ patient preference. Do not assume you know [what risks would be acceptable], ask a patient who is there now.”

Ethical challenges to pragmatic clinical studies

Jörgen Svidén, Administrative Director, Swedish Central Ethical Review Board, Stockholm, Sweden

Jörgen Svidén talked about ethical vetting of clinical trials. He explained that the scientific value must outweigh the harm for any clinical study, but he saw no particular ethical challenges to pragmatic clinical trials compared to conventional trials. “So why do people complain that the laws are preventing pragmatic clinical trials?” he asked. “If anything, pragmatic clinical trials normally study a larger population and therefore have a greater value, so they would possibly have better chances of approval from the ethical viewpoint.”

The use of electronic informed consent is highly desirable in pragmatic clinical trials. But is it compliant with the regulations? Informed consent is regulated in several places, Jörgen Svidén explained. The ethical review act requires consent to be voluntary, explicit, specific to particular research, and documented. Neither here, nor in the Medicinal Products Act, would electronic informed consent be of any issue. “But the Medicinal Product Agency’s guidelines state that the principles of GCP shall be applied,” said Jörgen Svidén. “And in these, it is specifically mentioned that an informed consent should be *written*.”

There is thus some confusion around what directive is valid, and if an electronic informed consent should be considered as written or not. Jörgen Svidén did not expect an

ethical review board to object to the use of electronic informed consent, but the Central Ethical Review Board has not formally tried the question.

Jörgen Svidén further stated that there are no particular ethical challenges regarding having more than one responsible research body or using registry data, as long as patients are able to opt out of the registries.

However, Jörgen Svidén noted that many registry-based randomised clinical trials (R-RCTs) use observational follow-up data from patients that have declined to participate in the interventional part of the study, and he did not think it was entirely clear if consent was needed for such use or not.

DANNOAC – a cluster-randomised registry-based study

Gunnar Gislason, Research Director, the Danish Heart Foundation, Copenhagen, Denmark

Gunnar Gislason told the story of the DANNOAC[19] study, designed to compare the four different non-vitamin K antagonist oral anticoagulants currently in use to reduce the risk of stroke in patients with atrial fibrillation. "The selected patients in randomised clinical trials do not match the populations we meet in the clinics afterwards," he said. "Elderly and patients with multiple comorbidities are often excluded."

The DANNOAC study was designed as a nation-wide cluster-randomised study. Hospital/clinic clusters would primarily prescribe one of the four NOACs for six months, then another one for six months and so on. The order of the four drugs would be different for the clusters. Importantly, individual patients would not shift drugs, but only the clusters. No written informed consent would be collected, but patients would be informed about the study and could choose to opt out. Follow-up of stroke, myocardial infarction, death, and major bleeding would be performed in nationwide registries. The protocol was reviewed and accepted by the regional ethics committee.

The study was initiated in one of the five planned regions in May 2017, but was stopped after only five days. The Danish National Committee on Health Research Ethics disagreed with the regional ethics committee and re-opened the discussion. The regional ethics committee then changed its previous decision and now requested individual written informed consent.

The DANNOAC study was closed in December 2017. "I tried to do a really pragmatic study that would benefit the patients," Gunnar Gislason said. "Patients have the right to know if the treatments are equally effective."

In reply to a question if it would have been impossible to obtain written consent, Gunnar Gislason said that it would have increased the costs, as it could not have been obtained during routine clinical practice. Gunnar Gislason believed that a study nurse would then have been needed at every site and feared that patients would have become more selected and inclusion would have been slower than expected.

19. DANNOAC https://hjerteforeningen.dk/dannoac/ ClinicalTrials.gov NCT03129490

"I think it is great to be able to host a conference like this in Uppsala. Any event of this kind renders attractivity to the industries here and to the city."

Christina Frimodig,
Managing Director, STUNS – Foundation for Collaboration between the Universities in Uppsala, Business, and the Public Sector, Uppsala, Sweden

Panel discussion

Rolf Gedeborg, Scientific Director for Epidemiology and Pharmacovigilance, Swedish MPA, Uppsala, Sweden
Gunnar Gislason, Research Director, the Danish Heart Foundation, Copenhagen, Denmark
Bettina Ryll, Chair, European Society for Medical Oncology (ESMO) Patient Advocates Working Group, Uppsala, Sweden
Jörgen Svidén, Administrative Director, Swedish Central Ethical Review Board, Stockholm, Sweden

The panel discussion revolved around the DANNOAC-related questions of cluster randomisation and informed consent in pragmatic clinical trials:

- A previously proposed Swedish academic RCT with informed consent comparing NOACs was planned to include 24,000 patients at an estimated cost of around 7.2 million euros, but that study was impossible to fund. Based on the failed attempts in Sweden and now in Denmark, a head-to-head comparison of NOACs is unlikely to ever be performed, leaving an important question unanswered.
- The new European clinical trial regulation opens up for clustering in the low intervention trial concept, but the cluster concept will probably not be implemented in Sweden.
- Is cluster randomisation only chosen in order to avoid informed consent?
  - Including consent in registry platform is as easy as cluster randomisation.
  - Consent is a burden for the clinician if no registry platform exists.
- For who do we want to have electronic informed consent?
  - Patients need a copy.
  - Doctors have to learn a new system and need to keep the consents on file.

Session III: Experiences from previous and current pragmatic clinical studies

Studying the effectiveness of a medicine pre-approval – the Salford lung study experience

Andrew Roddam, Vice President & Global Head Epidemiology, GlaxoSmithKline, Uxbridge, UK

The Salford study[20] measured effectiveness, the effect of a treatment given in routine clinical practice, already pre-approval. Around 7,000 patients with asthma or chronic obstructive pulmonary disease (COPD) were randomised to receive a new treatment or the usual treatment. Between the randomisation visit and the end of study visit, patients were under usual care for twelve months with constant real-time data collection of all interventions and safety monitoring. Inclusion and exclusion criteria were reduced to a minimum.

The Salford area was chosen for the study as it had a single well-developed system for electronic health records. Still, 15 different data streams were collected for each patient, totalling over 235 million data rows. Over 3,000 people were trained as part of the study.

The study was successful and showed that the new treatment was superior to the usual care, with no differences in safety.

Andrew Roddam pointed out that while the Salford study maintained scientific rigour through randomisation, active control design, and a robust primary endpoint it was also an enormous logistical effort. "It was a lot harder than what we thought when we started," he said, "and the back-end data aggregation was probably more complicated than it needed to be. But it was a learning exercise."

Andrew Roddam identified partnerships between the National Health Service, industry, and patients as a requirement for success, and emphasised the need to think about how infrastructure can be leveraged to answer research questions in the best way.

ViPViZA – communicating risk through images

Margareta Norberg, Assoc Professor, Dep of Public Health & Clinical Medicine, Umeå University, Umeå, Sweden

The Västerbotten Intervention Programme (ViP) is a long-term screening and cardiovascular disease (CVD) prevention program in primary care in Västerbotten in the north of Sweden. The core component of the study is the primary care health dialogue. ViP was launched in 1985 after studies had shown that Västerbotten had the highest premature mortality in cardiovascular diseases in Sweden during the 1970s.

Margareta Norberg said that the score charts usually used in Sweden and Europe to assess the statistical risk of CVD have low precision in low-risk individuals. Moreover, verbal communication of an abstract risk is challenging when trying to motivate behavioural changes to reduce individual risk. Socioeconomic and psychological factors also contribute to how a person perceives and responds to risk. "Low adherence is the big elephant in the room," said Margareta Norberg. "We have to think new. Can we try

20. The Salford study https://www.gsk.com/en-gb/media/press-releases/positive-results-from-pioneering-salford-lung-study-in-asthma-published-in-the-lancet-and-presented-at-european-respiratory-congress/ ClinicalTrials.gov NCT01706198

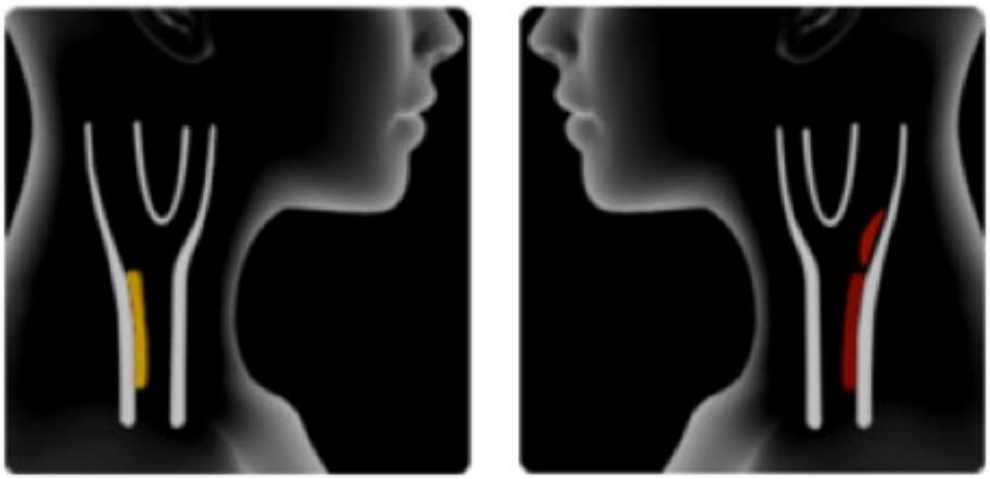

Figure 2. Example of stylised ultrasound images shown to participants in the ViPViZA intervention group.

other formats to communicate risk? A person-centered approach?"

The ongoing Visualisation of Atherosclerosis (ViZA) study[21] aims to evaluate atherosclerosis while it is still silent. One of the goals is to increase the motivation for CVD prevention and risk factor control in both patients and their primary care physicians. Three-thousand six-hundred healthy subjects from the ViP program at intermediate risk were invited for carotid artery ultrasound examination. Half of the participants, and their primary care physician, received pictorial information on the degree of atherosclerosis in the form of coloured 'traffic lights' and stylised ultrasound images (Figure 2). The other half of the participants did not receive any information on the ultrasound results. The study is still ongoing, but preliminary results indicate lower cholesterol levels and more prescribed lipid-lowering medication in the intervention group, as well as lifestyle modifications among the women in the intervention group.

Among facilitating factors for ViPViZA, Margareta Norberg highlighted that the study was set up within an existing structure, which made recruitment easy; that the data managers were experienced; and that the members of the steering group represented several specialties. Among the challenges, Margareta Norberg mentioned the extensive network; a relative lack of control; incomplete medical records; and ethical issues – are the controls, who do not receive any information about their ultrasound results, disadvantaged?

ALASCCA – low-dose aspirin in colorectal cancer patients

Anna Martling, Professor of Surgery, Dep of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Anna Martling talked about the experiences from setting up the ongoing ALASCCA study[22], which studies if low-dose aspirin treatment can increase survival in patients with colorectal cancer and somatic PI3K pathway mutations. Four-thousand patients will be recruited in 27 clinics in Sweden, Norway, and Denmark, and randomised to low-dose aspirin or placebo for three years, with time to recurrence as primary outcome.

21. ViPViZA https://www.vll.se/folkhalsoforskning/vasterbottens-halsoundersokningar-vhu-forskning/vipviza ClinicalTrials.gov NCT01849575
22. ALASCCA https://ki.se/en/mmk/alascca-study ClinicalTrials.gov NCT02647099

Previous retrospective studies have found associations between low-dose aspirin treatment and reduced risks of polyps, colorectal cancer, and relapse in patients with PI3K mutations. A possible mechanism of action is that colorectal cancers with PI3K mutations overexpress cyclooxygenase 2 (COX-2), which is in turn inhibited by aspirin.

ALASCCA is an R-RCT that employs the INCA cancer registry platform for randomization and follow-up. Patients already on aspirin for other reasons and patients without PI3K mutations are also followed. Participants are contacted by a research nurse every three months, and computer tomography examinations performed at one and three years as part of standard care will be employed for follow-up. The study thereby does not add any work for the doctors involved.

Anna Martling listed several success factors in setting up pragmatic clinical studies:

1. Build clinical networks to get faster and better access to patients. Listen and adjust to feedback.
2. Employ and be ready to pay for professionals and experts, but minimise all other costs.
3. Adapt the study design to healthcare processes to facilitate transition to clinical practice and increase the clinical value of the study.
4. Leverage existing infrastructure, reuse and educate instead of building new processes.

ADAPTABLE – reflections on a pragmatic trial

Matthew Roe, Professor of Medicine, Duke Clinical Research Institute, NC, US

The ongoing ADAPTABLE trial[23] aims to leverage available electronic health records and healthcare systems in the United States for patient recruitment and follow-up. Matthew Roe explained that the trial compares two different doses of aspirin in patients with atherosclerotic cardiovascular disease and at least one enrichment factor such as old age, diabetes, or high blood pressure. In parallel, follow-up frequencies of three or six months are compared with respect to patient adherence.

ADAPTABLE is funded through the Patient-Centered Outcomes Research Institute (PCORI)[24], and features heavy patient involvement. Patients have been involved at all stages of the trial, from protocol design to result dissemination planning; in all leadership groups; and they were integral in developing the consent form.

For patient recruitment, a common 'computable phenotype' was developed and used to query the various local electronic health records for potentially eligible patients. The clinics then contacted eligible patients directly via mail, e-mail, patient portals, or in-clinic during visits. Recruited patients were given a 'Golden Ticket' for access to the ADAPTABLE web portal. The patients were then to use the web portal to sign the electronic consent form, answer follow-up questionnaires, and report outcomes. Patient outcome reporting was crosschecked with electronic health records.

But patient recruitment has turned out to be more challenging than expected, said Matthew Roe. Whether the recruited patients actually entered their Golden Ticket number in the web portal has been highly dependent on the method of outreach. Almost 80% of in-clinic enrolled patients accessed the web portal, compared to under 40%

23. ADAPTABLE http://theaspirinstudy.org/ ClinicalTrials.gov NCT02697916
24. Patient-Centered Outcomes Research Insitute (PCORI) https://www.pcori.org/

of patients enrolled via e-mail or patient portals. Matthew Roe concluded that serial, sequenced follow-up contacts are needed for successful recruitment, but that the best method and frequency of remote outreach approaches still need to be determined.

Recently, a private health plan research partner began contributing to widespread outreach to eligible patients, and ADAPTABLE still aims to include 15,000 patients.

> *"We need to get even better at visualising the patient perspective and the value for patients with clinical trials, both in Sweden and internationally. I was delighted to learn that patient representatives participated in the conference, then you really show who you are working for."*
>
> Vivianne Macdisi,
> Member of the Regional Executive Committee, Uppsala, Sweden

Panel discussion

Anna Martling, Professor of Surgery, Dep of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
Margareta Norberg, Assoc Professor, Dep of Public Health & Clinical Medicine, Umeå University, Umeå, Sweden
Matthew Roe, Professor of Medicine, Duke Clinical Research Institute, NC, US

Comments on patient retention in pragmatic clinical trials
AM: We contacted the participants and collected the empty pill bottles. But you basically have to trust the patients.
MN: The participants regularly answered surveys so we could follow any changes in lifestyle, weight, and/or waist circumference.
MR: You have to touch base and stay in touch with the patients to ensure retention. This will be one of the challenges for pragmatic trials that run over a longer period of time.

Session IV: From epidemiology to healthcare – pitfalls and possibilities

What research results can be trusted?

Karl Michaëlsson, Professor of Medical Epidemiology, Dep of Surgical Sciences, Uppsala University, Uppsala, Sweden

Karl Michaëlsson sought to problematise the common notion that results from randomised trials are always preferable to results from non-randomised (often observational) studies. He used a series of examples to make the point that whether research results can be trusted or not depends on more than the chosen study design.

The first example regarded hormone replacement therapy in women and risk of cardiovascular disease. Observational studies had showed lower risk of cardiovascular disease with post-menopausal hormone replacement therapy, but a randomised trial instead showed an increased risk. Later analyses found that the discrepancies could largely be explained by differences in time since menopause in the participating women.

Secondly, observational studies had found associations between vitamin E supplementation and a reduced risk of coronary heart disease, which could not be replicated in subsequent RCTs. In fact, the dose-relationship curve is U-shaped – a modest dose of vitamin E reduces the risk of coronary heart disease, while very high intake increases the risk.

Thirdly, bisphosphonates are widely used to treat osteoporosis and prevent fractures, but have been associated with atypical femoral fractures after long-term use. However, both the existence and extent of this association differ across different study types. These differences seem to be at least partly due to imprecise definitions of atypical fractures, with some studies mixing normal and atypical fractures. "You need accuracy in your outcome as well as in your exposure," stated Karl Michaëlsson.

Lastly, Karl Michaëlsson discussed the important role of conflicts of interest in clinical research. "If you have industrial ties you will come up with different results compared to if you do not have industrial ties," he said. "We cannot put our heads in the sand and not consider this."

Balancing scientific certainty and medical need – the regulator's perspective

Rolf Gedeborg, Scientific Director for Epidemiology and Pharmacovigilance, Swedish MPA, Uppsala, Sweden

Rolf Gedeborg talked about the daily task of the Medical Products Agency (MPA) to balance scientific certainty vs medical need in the approval of new medicines. Not all market applications are supported by multiple well-designed, randomised, double-blind phase III clinical trials of long duration with extra long follow-up to obtain safety data. When has a new drug been through adequate testing?

The situation is particularly complicated for rare diseases and rare events. Rolf Gedeborg exemplified with a new treatment for Wolman's disease, a severe lipase deficiency where patients often die before eight months of age. In this case, efficacy and safety data from only 9 and 14 infants, respectively, was considered adequate. The drug

was however approved with the obligation to conduct a post-authorisation safety study.

But Rolf Gedeborg did not believe that more data is always better: "There is a strong focus on availability of data, not so much on how to make causal inferences from that data."

Rolf Gedeborg also objected to the claim that real-world evidence is always more reliable and representative than RCTs: "The beauty of randomisation is that it takes care of confounding, both known and unknown. Selection of patients in RCTs is only a problem if you have effect-modification, and there are selection problems also in real-world studies."

As one exemple of a selection problem in real-world studies, Rolf Gedeborg explained that when prescription registries are studied, in-hospital drug exposure is excluded, although that is when patients start new medications and are the most vulnerable.

In conclusion, Rolf Gedeborg wished for less focus on study labels and more focus on the fundamental scientific concepts: "At the MPA, we look at the totality of data and try to bring this together."

Health technology assessment challenges following RCT-driven regulatory work

Niklas Hedberg, Chief Pharmacist, Swedish Dental and Pharmaceuticals Benefits Agency, Stockholm, Sweden

The Swedish Dental and Pharmaceuticals Benefits Agency (TLV) among other things decides on pricing and reimbursement for pharmaceuticals. Niklas Hedberg said that TLV has identified an increasing discrepancy between the value of treatments in RCTs and in real life, with large knowledge gaps around effectiveness.

But real-world data (RWD) from follow-up studies also have challenges, Niklas Hedberg explained, such as:

- Access to data: what data is actually there and who can get access to it?
- Methodological challenges in the statistical analyses.
- Interpretation of data: the different financial interests of hospitals and companies can lead to different interpretations.

TLV therefore tries to create structures for re-evaluation of decisions as more data become available. The agency will run several pilot studies with regard to drug assessment and the use of RWD.

"The gap is widening between *can* it work and *will* it work. RCTs are better, bigger, and more expensive than ever, but what we need to assess, relative effectiveness, is less and less available," concluded Niklas Hedberg.

Epidemiological research and method development in industry

Gunnar Brobert, Director of Epidemiology, Bayer, Stockholm, Sweden. Replacing Montse Soriano Gabarro, Head of Epidemiology, Bayer

Epidemiological studies are used in all phases of drug development. Gunnar Brobert said that the focus of epidemiological studies performed in the pharmaceutical industry is shifting from safety towards effectiveness. Bayer mostly conducts observational studies, but Gunnar Brobert was interested in registry-based

studies: "We could look into many more compounds and do much more research in a much better way, but we are still trying to find the right study."

Gunnar Brobert highlighted two methodological development initiatives in epide-miological research: the FDA Sentinel[25] and the Observational Health Data Sciences and Informatics (OHDSI, pronounced 'Odyssey')[26]. Sentinel enables the FDA to collect large amounts of electronic healthcare data, such as electronic health records, insurance claims, and registries. FDA then analyses the data and sends out the results. OHDSI is an open, interdisciplinary, multi-stakeholder collaboration that aims to develop tools that can generate evidence in healthcare.

To increase the use of epidemiological data for key decision-making, Gunnar Brobert wanted:

- Robustness of methods, transparency, and reproducibility.
- Public-private partnerships for data access and use.
- Expansion of distributed database networks.
- Increased use and linkage of data sources.

Panel discussion

Rolf Gedeborg, Scientific Director for Epidemiology and Pharmacovigilance, Swedish MPA, Uppsala, Sweden
Niklas Hedberg, Chief Pharmacist, Swedish Dental and Pharmaceuticals Benefits Agency, Stockholm, Sweden
Karl Michaëlsson, Professor of Medical Epidemiology, Dep of Surgical Sciences, Uppsala University, Uppsala, Sweden
Gunnar Brobert, Director of Epidemiology, Bayer, Stockholm, Sweden

Do regulatory agencies want to be more involved in pre-planning of studies?

- Looking at protocols is an important part of the work at regulatory agencies.
- Pre-planning might help refine the research question.

Funding for national quality registries in Sweden is insecure, but regulatory agencies ask for more and better data…?

- We have a common responsibility to develop the registries. Government, MPA, and TLV need to discuss how the registries can be funded and used for more research.
- Neither the MPA nor TLV have the resources to fund research/data input, but TLV is willing to pay for analyses/data output.

Does Sweden have a responsibility to take the lead in developing pragmatic clinical studies?

NH: We have the opportunity to be among the first to find a responsible application for non-classical data and apply that to policy-making.

25. FDA Sentinel Initiative https://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
26. Observational Health Data Sciences and Informatics (OHDSI) https://ohdsi.org/

Session V: Overcoming challenges – solutions and opportunities

The Norwegian experience

Per Morten Sandset, Research and Innovation Director, Helse Sør-Øst, Oslo, Norway

In Norway, hospitals are required by law to conduct research as of the turn of the millenium. In return, health authorities are giving a lot of money to research. This is unique for Norway, and Per Morten Sandset said that research output has doubled in ten years as a result.

In the Southeastern Norway region, which covers over half of the Norwegian population, Per Morten Sandset said that the health authority has the ambition to include five per cent of the patients in research protocols. This is aligned to the ongoing development of indicators for how efficient hospitals are in recruiting patients to clinical trials – indicators that will be used for hospital funding in the future.

Regarding healthcare registries and digital infrastructure, Per Morten Sandset said that Norway is behind Denmark and Sweden, but regional and national strategies to improve quality and use of data are in place. Starting from 2016, the Norwegian government will fund comparative effectiveness studies of large importance for patient care, similarly to a Swedish initiative. "These are studies that would not be performed without this type of funding," said Per Morten Sandset.

In response to a question from the audience on how best to include patients from all Nordic countries in pragmatic trials, Per Morten Sandset said that joint study applications from several Nordic countries – applications sent simultaneously to the respective national funding bodies – would be looked upon favourably in Norway. "We have to think broader and use the initiatives that are already there, such as NordForsk. But *we* will have to do it, we cannot rely on anyone to do it for us," he concluded.

Real-world data (RWD) in clinical studies

Sreeram Ramagopalan, Director, Centre for Observational Research and Data Sciences, Bristol-Myers Squibb (BMS), Uxbridge, UK

Sreeram Ramagopalan showed that real-world data (RWD) from the Nordic countries, for example from national quality registries, have already proven useful for BMS. But he also said that although the data quality was generally excellent, BMS had experienced limitations in data access and timelines: "There is a vast difference in data accessibility between the Nordics and other countries, from the US and UK we can get more data faster. Also, the sample size is limited in the Nordic countries; it is not the place to go for rare diseases and rare events."

Sreeram Ramagopalan outlined the BMS RWD strategy, which includes steps to simplify clinical trial execution and to use patient-reported data to understand the patient perspective better.

In clinical trials, RWD could be applied in many ways:

- Before study: Optimise study design, refine inclusion and exclusion criteria, assess the representativeness of interested patients.
- During study: Pre-fill baseline data, use electronic consent, facilitate site selection/patient recruitment, live tracking, collect patient-reported outcomes. For single-arm trials, historical or synthetic control data could be used.
- After study: Continued tracking for safety and efficacy.

Sreeram Ramagopalan emphasised that for BMS to be able to fully leverage RWD, new capabilities are required and partnership development would be key: "We are trying to understand who has good data. We need to develop partnerships to get for example patient-reported outcomes. We could also develop partnerships with patient organisation to learn what issues are important to patients."

Sreeram Ramagopalan concluded that pragmatic trials have significant potential to fit in with BMS RWD strategy.

Combining registries and intelligent design – new Finnish legislation on secondary uses of health data and new EU regulation on clinical trials

Jukka Jokinen, Head of Impact Assessment Unit, National Institute for Health and Welfare in Finland, Helsinki, Finland

Finland has a long tradition of nation-wide health registries. As of July 2018, new laws come into force, broadening the possible secondary use of health data. Jukka Jokinen outlined the new National Electronic Patient Data Repository (KANTA)[27], which will attempt to solve the problem of scattered healthcare records. KANTA will collect health data from various sources into a single patient management service. It will cater for primary treatment use, including mandatory electronic prescriptions, and secondary research use with built-in consent management. Permissions, data requests etc will be handled in a central service operator model.

Jukka Jokinen also saw great possibilities with the new EU regulation on clinical trials, particularly the low intervention trial concept. "This will open up a whole new avenue of what we think is feasible," he said.

In relation to the DANNOAC presentation by Gunnar Gislason, Jukka Jokinen pointed out that the new EU regulation specifically mentions cluster randomisation. But he did not agree with the previously raised concerns about cluster randomisation and informed consent: "The ultimate points are that we will study established treatments that the patients will get anyway, and for that we need large trials, which are only feasible with cluster randomisation. I think there are no ethical grounds to oppose low intervention trials of established treatments."

In response to a question from the audience on when applications for KANTA data can be sent in, Jukka Jokinen said that e-prescription data are available immediately, but for the rest they will pilot how to extract data in the best way. "We already have

27. KANTA
http://www.finlandhealth.fi/-/finland-s-national-health-data-service-benefits-citizens-healthcare-professionals-pharmacies-and-the-society

more than a billion records. Low-hanging fruit will be the first step, and then we will make incremental steps from there."

Panel discussion

Jukka Jokinen, Head of Impact Assessment Unit, National Institute for Health and Welfare in Finland, Helsinki, Finland
Sreeram Ramagopalan, Director, Centre for Observational Research and Data Sciences, Bristol-Myers Squibb, Uxbridge, UK
Per Morten Sandset, Research and Innovation Director, Helse Sør-Øst, Oslo, Norway

Industry interaction with patient organizations (SR)

- Patient-created data repositories (intended to accelerate research) are of low quality, but industry is interested if patient groups want to partner and develop them.
- Industry representatives join Facebook groups to interact with patient organisations.

Free drugs in pragmatic clinical trials
SR: There are models of doing this. For registrational pragmatic clinical trials, BMS provides drug for free.
PMS: In Norway, governmental funding includes drug, patient visits etc.

How competitive are we in the Nordics?

- Still superior in Europe with respect to registry data quality, but it takes longer and longer to deliver data.
- The upcoming Finnish legislation contains a time limit of 2–3 months for providing data.

Session VI: Synergies in the Nordic countries

Nordic guidelines for registry-based randomised clinical trials (R-RCT)

Peter Hedman, Director of Development, UCR, Uppsala, Sweden

Registry-based randomised clinical trials (R-RCT)[28] are clinical trials that use registries for patient inclusion, randomisation, and/or follow-up. UCR has developed the R-RCT concept and is now coordinating the development of Swedish national R-RCT guidelines[29] together with Forum Uppsala-Örebro and Clinical Studies Sweden[30]. "We have a lot of experience and the technical framework," said Peter Hedman. "We would like to share this with others so they can do these pragmatic trials as well."

R-RCTs are often described as very easy to perform. Peter Hedman wanted to modify this picture slightly: "R-RCTs are really simple *when they are in place,* but there is a lot of work before that. There are also different processes and new roles that you have to include compared to a conventional trial. But once in place, you fill in what you regularly enter in the registry and just click randomise."

The national guidelines work is run in collaboration with other registry centers in Sweden and supported by the Swedish research council through Clinical Studies Sweden. The background is the need for faster, smarter, and less expensive trials; the demand for more pragmatic clinical trials; and the desire to do clinical trials that are of interest to patients but not necessarily to the pharmaceutical industry. "We are not going to do the same amount of studies for less money," said Peter Hedman, "we will do more studies for the same money."

Peter Hedman also explained that although the R-RCTs performed so far have all used national quality registries, this is not a requirement: "Technically speaking, any structured dataset can be used in an R-RCT."

The Swedish national guidelines for R-RCT will include:

- When you should – and should not – use R-RCT
- Different types of R-RCTs
- How to adapt study protocols for R-RCT
- Work process for R-RCT
- Templates
- Documentation
- Technical framework

The Swedish national guidelines for R-RCT are expected to be completed during early 2018. Peter Hedman said he then wanted to adapt them to make Nordic guidelines. "I do not think it will be a lot of work. And it will definitely be worth it," he said, emphasising the similar infrastructures and laws in the Nordic countries. "If you want to avoid all the mistakes we have made, my e-mail is open and we can take it from there."

28. Registry-based Randomised Clinical Trials (R-RCT) http://www.ucr.uu.se/en/services/r-rct
29. Swedish national guidelines for R-RCT https://www.kliniskastudier.se/english/development-initiatives/national-standard-r-rct-.html
30. Clinical Studies Sweden https://www.kliniskastudier.se/english.html

Embedded pragmatic clinical trials – triumphs and tribulations

Joakim Ramsberg, Visiting Lecturer, Dep of Population Medicine, Harvard Medical School, and Principal Secretary, Government commission on pharmaceuticals, Stockholm, Sweden

"In general, there is a troubling lack of evidence in decision-making," said Joakim Ramsberg.

He explained that while RCTs are considered the gold standard in decision-making, they by design have excellent internal but lower external validity. Pragmatic clinical trials (PCT), on the other hand, could generate strong randomised evidence with high external validity. "But if they are so good," asked Joakim Ramsberg, "why are they not used more?"

Joakim Ramsberg recently reviewed 108 embedded pragmatic trials and interviewed 30 professionals in the US with PCT experience to identify common facilitators and barriers. He found that PCTs were conducted in all disease areas, and that as much as 75% of the trials were at least partially performed in the primary care setting. The median cost per included patient was $97, but Joakim Ramsberg added that the true costs for embedded PCTs, not only the incremental costs, are hard to calculate.

Among the key factors for successful PCTs, Joakim Ramsberg listed good organisational bandwidth, sufficient research funding, and well-developed IT structures. Examples of challenges were inadequate data, misaligned structures, and unclear research governance.

In conclusion, Joakim Ramsberg emphasised that embedded PCTs can help find timely answers in healthcare, but that the right questions have to be asked and the studies have to be designed so they do not disturb healthcare delivery.

Nordic Trial Alliance – Nordic cooperation in clinical research

Pierre Lafolie, Project Leader, Nordic Trial Alliance, Stockholm, Sweden

The Nordic Trial Alliance works to promote cooperation in clinical research among the Nordic countries. Pierre Lafolie listed some examples of ongoing activities:

- Create a common Nordic medical ethics committee and/or mutual recognition of ethical approvals from other Nordic countries.
- Analyse how the Nordic area could develop into a 'hotspot' for life sciences.
- Support the development of pragmatic clinical trials, starting with the current meeting.

Pierre Lafolie believed that better collaboration is needed between conductors of pragmatic and conventional trials so the different trials can complement rather than compete with each other: "The Nordic countries have a window here if we can collaborate. There is movement in large countries such as Germany and France, but no other region than the Nordic can provide the whole chain from innovation to life cycle management."

In response to a question from the audience on how we can put pressure on politicians and decision-makers to resolve legal and practical issues around pragmatic studies, Pierre Lafolie said that the only way forward is to create a win-win situation: "We need to talk, calculate, and provide evidence. The Nordic countries have different skills, and all countries could add to a good blend."

"I would like people to leave the conference with the feeling that there are no opposite sides. Pragmatic and conventional studies answer different questions and both are needed. I would also like the [Medical Products] Agency to not be perceived as a stopping device but as an enabler for clinical research."

Marie Gårdmark, Director,
Swedish Medical Products Agency, Uppsala, Sweden

Panel discussion

Peter Hedman, Director of Development, UCR, Uppsala, Sweden
Pierre Lafolie, Project Leader, Nordic Trial Alliance
Joakim Ramsberg, Visiting Lecturer, Dep of Population Medicine, Harvard Medical School, and Principal Secretary, Government commission on pharmaceuticals, Stockholm, Sweden

The panel discussion mainly revolved around registry-based trials:

How can we increase R-RCT use and make the tool more accessible?
PH: It is a challenge to get researchers and doctors to agree on what to study. You have to decide what you need, what type of data you need, where the data is and in what shape it is. Then we can look at the possibilities of accessing that data. It does not have to be that complicated.

Are all Swedish registries ready for R-RCT?
PH: No, not all registries are ready. It is hard to generalise; we need to look at the study *and* the registry to see if the registry in question can be used in the intended way.

Would it be possible to combine data from the Swedish national quality registries with KANTA or Danish systems, if legal and collaborative aspects were in place?
PH: Yes. We have gathered data over the Internet for 20 years; the technical challenge is not that big. Any system developer can use our systems; the hard part is to ask the right questions.
PL: The legislative aspects are hard to solve. We need to provide grants to people to explore these aspects.

Are electronic health records (EHR) as accessible as registries?
PH: Technically yes, but EHRs are more difficult to use for R-RCT because the data is less structured than in the registries. We are currently working on projects in primary care using EHRs.

How can we work to get acceptance for an R-RCT among clinicians?

- Create discussion, invite proposals, ask registry steering committees to list important questions.
- Involve patients and industry to discuss. Keep it simple the first time.
- Get consensus among specialists in a given field that a particular question is the one we should investigate at the moment. It is better to agree to study the second most important question if it is not feasible to address the most important question right now.
- Remember that the quality registries are national infrastructures, they are not the property of steering committees.

How do we move forward with pragmatic clinical studies in the Nordic countries?

JR: We need to create a research and development function for the Nordic countries, with real money to invest in important questions to make healthcare policies more evidence-based.

PL: We need more collaboration on the Nordic level. We have a responsibility to provide patients with new treatment as soon as possible. We must not think we can do everything ourselves, we need to reach out and truly collaborate.

PH: We need to reach out to our neighbours. It is just a matter of doing it.

Closing remarks

Jonas Oldgren, Executive Director of UCR, concluded that 'pragmatic clinical studies are here to stay.'

He listed some of the areas where improvement is needed:

- Methodological, legal, and ethical issues need to be resolved.
- Funding issues and hidden costs for pragmatic clinical studies within regular healthcare need solutions.
- Are all quality registry steering committees really on their toes to do pragmatic trials in their registries?
- Cross-border collaboration is important because we have so many similarities in the Nordic countries and share the problem of insufficient population sizes.
- Politicians, industry, and academic researchers need to be made aware of the opportunities with pragmatic clinical trials.

The conference website (npcs.se) will remain accessible. Here, relevant updates, such as the Swedish national guidelines for R-RCTs and other publications, will be posted. Flagging of a possible follow-up conference or other related events and activities will also be published here.

Lastly, Jonas Oldgren thanked the organising committee headed by Susanna Thörnqvist, and hoped that the productive discussions would continue after the conference.

Exhibitors

Elsevier MACRO
https://www.elsevier.com/solutions/macro

IQVIA
https://www.iqvia.com/

World Courier
https://www.worldcourier.com/

Forum Uppsala–Örebro is part of Clinical Studies Sweden, a collaboration between the Swedish Research Council and Sweden's healthcare regions. Forum Uppsala–Örebro is the regional node for three county councils and four regions, the county councils Dalarna, Sörmland and Värmland and the regions Uppsala, Örebro, Västmanland and Gävleborg. The task is to collaborate with and support all the actors involved in clinical studies in the healthcare region.

UCR (Uppsala Clinical Research Center) is an extensive resource for clinical research regionally, throughout Sweden, and internationally. We are proud that our work has contributed to improving the health of people throughout the world, and we strive continuously to increase medical knowledge and improve health through research and quality monitoring.

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