Report RSNN Annual Workshop 18-11-2025: Single Arm Trials

The workshop kicked off with welcoming words from Peter Mol (UMCG/CBG-MEB), introducing the goals of the workshop: exploring Single Arm Trials (SATs) from multiple perspectives and sharing experiences from experts across science, regulation and industry.

As the first presenter, **Harm van Tinteren** (Princess Maxima Center for Pediatric Oncology) shared his insights on SATs drawing from his many years of experience as a statistician in oncology research. He began his presentation by defining a SAT as a clinical trial design in which all participants receive the same treatment, without any concurrent control or comparison group. He described circumstances in which SATs may be appropriate: rare diseases, conditions with a high unmet medical need or life-threatening conditions, interventions with a strong biological rationale, situations lacking effective treatments, or settings with ethical constraints on randomization. In such cases, external control arms, based on historical, real-world, published or synthetic data, can provide valuable comparative insights. However, provided that rigorous statistical methods and sensitivity analyses are applied to ensure the robustness of the findings. He concluded by stressing the importance of maintaining statistical rigor and methodological transparency in SATs, ensuring that design, conduct, analysis, and reporting follow Good Clinical Practice standards.

Representing CBG-MEB, **Emmely de Vries** gave a regulatory perspective on SATs and the implications of the benefits and risks. She emphasized that SATs carry inherent uncertainties and potential biases due to their lack of randomization, concurrent control arms, and blinding, complicating the interpretation of treatment effects, safety profiles and external validity. For SATs serving as pivotal evidence in marketing authorization applications (MAAs), success criteria should be clearly defined in advance and primary endpoints should be objective and capable of capturing treatment effects. From her own experience and research, she highlighted that SATs in almost all cases served as pivotal evidence for approval of Advanced Therapy Medicinal Products (ATMPs) and are expected to remain the key source of evidence for these products. Looking ahead, she emphasized the importance of regulatory guidance and that currently, an EMA reflection paper on external controls is being written.

Scott Jung (Kite Pharma) discussed the use of surrogate endpoints in clinical trials, which can be measured earlier or more easily than traditional outcomes such as survival or quality of life. He pointed out that the relationship between surrogate endpoints and the true clinical benefits must be well understood and ideally validated. Also, surrogate endpoints like progression free survival (PFS) or overall response rate (ORR), require careful statistical handling, including censoring and timing of assessments, to ensure robust interpretation. To help contextualise results from SATs, advanced approaches such as synthetic control arms, real-world data or AI-generated "digital twins" can help.

Referring to her work as a medical oncologist specializing in colorectal carcinoma (CRC), **Miriam Koopman** (University Medical Centre Utrecht) stated that everything she does is aimed at being able to give every (CRC) patient a personalized treatment advice, irrespective of hospital, region or country. However, this is not possible yet, as current guidelines are based on trials that include only a narrow and often fitter subset of the real-world population, while ongoing advances in molecular profiling are increasing patient heterogeneity. Drawing from her experiences as chair of the ESMO Working Group on Real-World Data, she showed survey results indicating that the trust regulators and health care professionals have in real-world data, depends on the quality of the data. Giving examples from the Prospective Dutch Colorectal Cancer Cohort study, she demonstrated how large observational cohorts can complement trial data. To fully leverage real world data, she advocates for standardized endpoints, consistent data definitions, and integration of AI to extract data from electronic health records. She concluded by discussing her envisioning of a learning healthcare system where real-time RWD, AI and standardized processes enable individualized, patient-centred oncology care.

Frank Hulstaert (KCE) provided an HTA-perspective on SATs, emphasizing how HTA bodies differ from regulators. He noted that regulators have a centralised European system evaluating benefit-risk, whereas HTA bodies look for comparative evidence versus standard care (or best supportive care). HTA decisions remain largely national, although increasing alignment is emerging through joint scientific consultations and joint clinical assessments. External control arms, when based on real-world data, can suffer from missing variables and varying data quality. The lack of randomisation may lead to incorrect conclusions about treatment benefit. Frank mentioned that EMA and HTA agencies have collaborated recently to develop clearer guidance on study designs, endpoints and their statistical analysis. He concluded that randomization early in de clinical development program, more pragmatic randomized designs, registry-based trials and trials within cohorts could strengthen comparative evidence development and reduce uncertainty for payers and patients.

An additional HTA-perspective, focussing on the Dutch HTA process, was provided by **Lydia Stiny**, representing Zorginstituut Nederland (Dutch National HTA-body). She explained that the primary criterion in their evaluation is effectiveness compared to the Dutch standard of care, which serves as a "knockout" criterion: in case the assessed intervention is not as effective or more effective than the current standard of care, the assessment cannot proceed advice for reimbursement is negative and the remaining criteria are not assessed. The framework that is being used in the Netherlands includes categorisation of the quality of evidence ofr desirable and undesirable effects. She stated that SATs are generally treated similarly toas observational data: they receive a low evidence rating due to high risk of bias caused by lack of randomization and thus potential confounding. However, they SATs are not automatically rejected because factors like disease rarity, absence of alternative therapies, and feasibility of randomized trials are considered as well. Moreover, SAT-evidence is generally indirectly compared with an external control cohort. Unfortunately, these indirect comparisons are not always transparent and sensitivity analyses are often not published. may be supplemented with indirect comparisons, sensitivity analyses, or external control data where possible. Lydia emphasized that SATs can be used in certain situations, but they require case-by-case consideration and careful interpretation.

The workshop was concluded by **Daan Breederveld**, who shared a dual perspective as both a participant of a SAT and having a background as a clinician. In 2019, he participated in a trial investigating gene therapy for haemophilia B and shared his decision-making process about whether to participate. With his decision he hoped to contribute to scientific knowledge that could help future patients, while also seeking personal benefit in terms of freedom from ongoing injections with factor replacement therapy. He pointed out that the certainty of receiving the treatment was a crucial factor in his willingness to participate. From a broader perspective, Daan stressed the importance of patient-centred endpoints in trials, arguing that both clinical outcomes and patient-reported outcomes are essential to capture the real-world impact of therapies. He concluded his presentation by arguing that understanding of the perspectives of patients, their individual context, and the practicalities of trial participation is crucial to designing meaningful studies that accurately assess treatment effectiveness.

The workshop provided a view on SATs from multiple perspectives: covering methodology, regulatory requirements, HTA and patient perspectives. Although SATs can provide critical evidence for rare diseases or in settings of high unmet medical needs, they require careful design and rigorous statistical methods. From a regulatory and HTA view, clear definitions of success criteria and objective endpoints are warranted. Several options to contextualize results from SATs were addressed, such as the use of Real-World Data, synthetic control arms or AI-generated 'digital twins'. To fully leverage Real-World data, endpoints should be

standardized and consistent data definitions should be in place. From a patient perspective, a single arm design can have crucial influence on willingness to participate. Overall, the workshop offered valuable insights into the challenges and opportunities surrounding SATs and the perspectives of varying stakeholders on their use.