Sylvan Green Award Winners

2026

Author: Nurulamin Noor
Institution: University of Cambridge
Title: PROFILE Trial – Disease Modification With Early Treatment in Newly-Diagnosed Crohn's Disease

Abstract:

Background Management strategies and clinical outcomes are highly heterogenous in patients newly-diagnosed with Crohn's disease. Despite the availability of more treatment options, a "step-up" approach to care has persisted as the global standard of care, with sequential escalation of treatment in response to disease flares. We evaluated the use of top-down (i.e., early combined immunosuppression with infliximab and immunomodulator) versus accelerated step-up (conventional) treatment strategies in adult patients newly-diagnosed with active Crohn's disease.

Methods PROFILE (PRedicting Outcomes For Crohn's disease using a moLecular biomarker, ISRCTN11808228) was an investigator-initiated, pragmatic, multicentre, open-label, biomarker-stratified, randomised controlled trial that enrolled adults with newly diagnosed active Crohn's disease (Harvey-Bradshaw Index ?7, either elevated C-reactive protein or faecal calprotectin or both, and endoscopic evidence of active inflammation). Patients were randomly assigned 1:1 to top-down or accelerated step-up treatment. The primary endpoint was sustained steroid-free and surgery-free remission at the end of one year. Analyses were done in the full analysis (intention-to-treat) population. A cost-effectiveness analysis was conducted using one-year outcomes and simulating a time horizon of 5 years using a Markov model. While additional five-year follow-up data has been collected as part of the PROFILE long-term extension study.

Results Between 2018, and 2022, 386 patients (mean age 33·6 years [SD 13·2]; 179 [46%] female, 207 [54%] male) were randomised: 193 to the top-down group and 193 to the accelerated step-up group. Median time from diagnosis to trial enrolment was 12 days (range 0–191). Primary outcome data were available for 379 participants (189 in the top-down group; 190 in the accelerated step-up group). Sustained steroid-free and surgery-free remission was significantly more frequent in the top-down group than in the accelerated step-up group (149 [79%] of 189 patients vs 29 [15%] of 190 patients, absolute difference 64 percentage points, 95% CI 57 to 72; p<0·0001). There were fewer adverse events and serious adverse events in the top-down group than in the accelerated step-up group (adverse events: 168 vs 315; serious adverse events: 15 vs 42), (including less disease flares and less serious infections). In addition there was a tenfold reduction in need for urgent abdominal surgery (odds ratio=0·095; 95% CI=0.001–0.505). Top-down therapy was also cost-effective, with Markov modelling to a 5-year time horizon being dominant with gain of QALYs of 0.17 per patient and saving of up to £10,059 per patient over 5 years. Median 3-year follow-up data from 361 patients participating in the long-term extension study show persistence of lower abdominal surgery in the top-down arm compared accelerated step-up group (19 vs 3).

Conclusions Early, effective "top-down" treatment with combination infliximab plus immunomodulator achieved substantially better efficacy and safety outcomes at one year than standard of care treatment. Early, effective control of inflammation from diagnosis was also demonstrated to be cost-effective (dominant). Initial three-year follow-up data from the long-term extension study also demonstrate the benefits of early, effective "top-down" therapy are sustained over time. Early, effective "top-down" treatment should now be considered the global standard of care for patients newly-diagnosed with active Crohn's disease.

2025

Author: Ryan Berry
Institution: Harvard College; Michigan State University

Title: Pioneering Physician-Led Trials: Transforming Treatment for Adrenal Insufficiency and Beyond

Abstract:

Physicians frequently recognize potential treatments for conditions that lack sufficient market size to attract industry-sponsored trials. These opportunities remain unvalidated due to significant barriers, including complex regulatory pathways, funding limitations, and the absence of commercial incentives. This study presents an innovative framework for practitioner-led clinical trials that leverage existing FDA-approved devices and real-world data, enabling impactful research independent of industry support. Using the case of continuous subcutaneous hydrocortisone infusion for adrenal insufficiency, the trial exemplifies how practitioners can navigate these challenges.

Subcutaneous infusion devices, approved for insulin delivery, are ideal for repurposing due to their established safety profiles and versatility. In adrenal insufficiency, standard oral hydrocortisone therapy often results in peaks and troughs, requiring supra-physiologic doses during troughs to stabilize patients. These fluctuations compromise quality of life and elevate long-term health risks. Continuous subcutaneous infusion offers a more physiologic delivery, stabilizing cortisol levels, reducing hospitalizations, and improving patient-reported outcomes.

Our trial design incorporates retrospective electronic medical record data collected and analyzed by our team to inform eligibility criteria and outcome measures. The primary outcomes include a reduction in hospitalization rates for adrenal crises and improvements in quality of life, assessed using validated questionnaires. Secondary outcomes evaluate fatigue levels, adjustments in daily hydrocortisone dose, serum adrenocorticotropic hormone levels, adverse events, and device-related complications. By leveraging adaptive design elements and real-world data, this framework provides a scalable, resource-efficient approach to trial execution.

The trial's design highlights how funding mechanisms such as PAS-23-086 Small R01 can support small-scale studies, demonstrating that properly constructed trials can yield data robust enough for treatment approval and insurance coverage. Beyond adrenal insufficiency, this model serves as a template for other conditions where potential treatments exist but lack industry interest due to limited market size. The framework prepares for future needs as data analytics continue to identify novel treatment applications that may not attract commercial investment.

This practitioner-led approach not only bridges the gap between clinical observation and formal evidence generation but also ensures that overlooked therapies can be validated and brought to patients. By addressing current and future challenges, this model shapes a path for impactful, sustainable research that adapts to the evolving landscape of clinical science, ultimately expanding treatment options and improving patient care.

2024

Author: Kenichi Nakamura
Institution: National Cancer Center Hospital
Title: Innovating Oncology Clinical Trials: A Leap Towards Fully Decentralized Trials in Japan

Abstract:

In oncology, Japan's shift to Fully Decentralized Clinical Trials (DCTs) represents a significant evolution, addressing the clear differences in clinical trial access, especially in remote areas. Despite comprehensive genomic profiling tests being covered under national health insurance, only a small percentage of patients (9.4%) have been able to access matched treatments. The pandemic's impact, highlighting these disparities, led to the legal sanctioning of telemedicine, paving the way for the inception of DCTs.

The DCT model, piloted by the National Cancer Center Hospital (NCCH) in Tokyo, facilitates telemedicine for patients in distant regions. These patients visit local hospitals, referred to as partner sites, for necessary examinations like blood tests and CT/MRI. The results are then shared with NCCH, where investigators make key decisions regarding patient eligibility and treatment continuation. This model integrates e-consent, telemedicine, and data-sharing platforms. A

physician at the partner site supports the patient during telemedicine sessions, ensuring comfort and smooth information exchange. Study drugs in this model are oral since they can be delivered directly from NCCH to the patient's home.

This DCT approach significantly improves clinical trial access for distant regions. Partner sites, handling delegated tasks, simplify ethical reviews, education, and monitoring. A notable benefit is faster patient recruitment, with NCCH able to reach patients nationwide, not just in Tokyo. This is particularly advantageous for trials involving rare cancers and conditions where consistent patient recruitment is challenging. Additionally, DCTs potentially reduce overall clinical trial costs through reduced monitoring expenses and shortened recruitment periods, achieved by remotely sharing data from partner sites.

The TAZETTA trial serves as a case study, demonstrating DCTs' effectiveness in oncology. This phase II trial for Tazemetostat, targeting patients with rare cancers like unresectable or metastatic epithelioid sarcoma, underscores the suitability of DCTs for trials involving oral medications with established safety profiles.

Multiple regulatory issues have been discussed and resolved before starting DCTs including; i) What kind of tasks can be delegated to partner sites? ii) To what extent does NCC need to give training/information to partner sites, iii) Is multi-factor authentication required even when CRC ensures and records the process that patients themselves give eConsent? iv) Is direct drug shipment from the depot to the patient's home possible under the supervision of the sponsor? etc. Ongoing developments in regulations are closely monitored to ensure compliance and safeguard patient interests.

NCCH is extending the scope of DCTs internationally, with a partnership with Thailand. At first, it was difficult to realize the cross-border fully remote DCT model, because a local medical license was required for Japanese medical oncologists to conduct telemedicine for patients living in Thailand. However, the Thai Ministry of Health finally agreed on issuing temporary medical licenses to medical oncologists for realizing cross-border DCT and has made a memorandum of understanding with NCCH. This collaboration highlights the potential of DCTs in international trials and addresses challenges such as regulatory discrepancies and licensing issues.

2023

Author: Su Jin Kang
Institution: Imperial College London
Title: Biostatistical Models to Investigate Physiological Mediators Regarding Cognition on Cardio-Metabolic Risk Factors in the Middle-Aged: The CARDIA Study

Abstract:
Background: While there is mounting evidence of an association between cardiovascular disease and brain health, the evidence from longitudinal cohort studies is currently inconclusive, in part because of a lack of studies with appropriate physiological measures. The aim of the study is to investigate physiological mediators regarding cognition given a cardio-metabolic risk using the multivariate biostatical models.

Materials and methods: The present study focuses on sub-cohort data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study using targeted metabolomics data by high-resolution nuclear magnetic resonance spectroscopy and liquid-chromatography mass spectrometry for 606 participants, and the brain magnetic resonance imaging (MRI) data for 280 participants aged 48-60 years at Year 30 (2015-16). In addition, the complete brain data for 185 participants were available at Year 25 (2010-11). A path analysis was conducted to investigate mediators of adjusted cognition on a cardio-metabolic factor measured at Year 30. In addition, Bayesian multilevel models were employed to examine cognitive decline measured at Year 25 and Year 30.

Results: Phenylalanine, aminoadipic acid, and tryptophan were mediators showing positive associations on fasting glucose in terms of hyperglycaemia, while indole-3-acetic acid showed a negative association. Cerebral blood flow in temporal

lobe white matter (WM) left and left entorhinal area showed negative associations on waist circumference in terms of (abdominal) obesity in the cohort. For the cognitive impaired individuals, identified as physiological markers included significant exposures (i.e. race, education, family income, sex, age, center for epidemiologic studies-depression, smoking), metabolites (i.e. glycine, methionine, aminoadipic acid, tryptophan and kynurenine) and brain MRI-derived parameters (i.e. the number of activated voxels within temporal lobe, right anterior cingulate gyrus and fractional anisotropy in right medial frontal cortex).

Conclusions: The study employed a fusion analytic method for the different types or levels of data from the longitudinal epidemiological study. The multiple biostatistical analysis approach applied here with a follow-up study may be able to recognise complex multivariate epidemiologic, pathologic, and phenotypic relationships across the disease networks that are yet unidentified.

2022

Author: Andrea Viecelli
Institution: Princess Alexandra Hospital
Title: Enhancing Patient-Partnership in Clinical Trials

Abstract:
Background and aim: Involving consumers in the design and conduct of clinical trials is increasingly recognised as important and potentially transformational. We aimed to improve the relevance, efficiency and value of nephrology clinical trials by implementing a range of approaches to engage consumers across all stages of trial conduct.

Method: The Australasian Kidney Trials Network (AKTN) has taken a structured, multipronged approach to substantially augment consumer engagement through: Consumer representation on all research-related committees; Formation of a Consumer Advisory Board for consumer training and trial-specific activities; Consumer representation on trial grant applications and Trial-specific consumer workshops to define outcomes, interventions, recruitment strategies, dissemination and implementation plans.

Results: Since 2019, two consumers have been recruited to the AKTN scientific committee and 100% (7/7) of initiated trials had at least two consumers on national trial steering committees. A diverse 10-member consumer advisory board was established to provide consumer training (e.g. introduction to clinical trials, a 2-hour Good Clinical Practice Workshop), a “buddy support system” for new consumers and input into all consumer-facing trial materials and protocols. Six successful trial grant submissions had at least one consumer listed as Chief or Associate Investigator. Seven national multistakeholder workshops including 173 patients and caregivers have been conducted to define and implement the most relevant trial outcomes (INCH-HD, VALID), interventions (M-FIT), recruitment and retention (M-FIT, VALID), and dissemination and implementation strategies (CKD-FIX, IMPROVE-CKD). Consumer involvement has increased the relevance of trials through selection of patient-relevant outcomes and interventions, patient-friendly trial conduct (e.g. lay language trial summaries, minimising extra trial visits, e-consent option, audio-visual trial information, data completion on own electronic devices), and dissemination (patient-led audio-visual and written trial reports disseminated via patient-channels, consumer-led presentations and publications).

Conclusion: Engaging consumers in a supportive, structured way with key roles and activities has greatly enhanced the relevance, efficiency and implementability of AKTN-led clinical trials.

2021

Author: Lara Philipps
Institution: Institute of Cancer Research – Clinical Trials Statistics Unit
Title: Study within a trial comparing electronic versus paper patient reported outcome collection
Abstract:

Introduction:

Within oncology trials patient perspective and survivorship effects are important considerations in evaluating new treatments (2). Patient-reported outcomes (PRO) are collected using validated questionnaires that measure the impact of treatment and health conditions on quality of life.

The majority of cancer clinical trials currently utilise paper questionnaires, a time-consuming data collection process. Streamlining via electronically-collected PRO (ePRO) may improve convenience, efficiency and lead to more complete data (3)(4).

Although ePRO have been widely studied in the general clinical setting there is little published literature demonstrating that they are as effective as paper PRO within clinical trials with the associated additional research ethics, governance and regulatory requirements. Our study-within-a-trial (SWAT) will test implementation of ePRO collection.

Methodology:

A survey has been collaboratively designed with the charity Independent Cancer Patient's Voice assessing attitudes regarding health questionnaires amongst members of the general public. Survey participants may opt to participate in a focus group supporting development of the SWAT.

The SWAT will compare electronic versus paper PRO collection within randomised controlled cancer trials. The design is a partially-randomised patient preference trial to ensure that "real-world" data is collected and to prevent participants being excluded due to lack of internet access.

Eligible patients will be participants of a host trial within which the SWAT is embedded. They will either be randomly allocated to electronic versus paper PRO, or will receive their preferred modality if they are unsuitable to be randomised. All participants will complete a paper baseline questionnaire and will then receive questionnaires either electronically via a secure online database or on paper at appropriate time points for the host trial up to 12 months. All participants will receive a paper questionnaire assessing satisfaction of the modality of PRO completion at 14 months post-enrolment.

The primary endpoint is patient compliance (% questionnaires returned out of those expected) at the host trial's first post-intervention PRO time point, and the aim is to test for non-inferiority of electronic versus paper PRO.

It is unknown what proportion of participants will accept randomisation versus having a preference. Therefore, the sample size required for the randomised cohort has been estimated, and the numbers entering the preference versus sample size required for the randomised cohort has been estimated, and the numbers entering the preference versus randomised parts of the SWAT will be monitored. Currently, compliance with paper questionnaires at the first post-intervention time point in Institute of Cancer Research Clinical Trials Statistical Unit trials is around 90%. With this assumption, 244 patients (randomised 1:1) are required to exclude compliance rates with ePRO <80% (i.e. 10% non-inferiority margin), with 80% power and 1-sided alpha=0.05.

Secondary endpoints include comparison of distributions of domain scores and item responses between electronic and paper questionnaires at key time points and in relation to baseline paper questionnaires, compliance at further time points within the host trial, data completeness (% of completed items within the questionnaire), and patient satisfaction with both modalities.

Discussion:

EPRO could significantly improve the patient experience within clinical trials. Our work aims to show evidence of non-

inferiority of ePRO compliance as part of a roll-out within clinical trials.

2020

Author: Chengwu Yang
Institution: College of Dentistry, New York University
Title: Connecting randomized controlled trials (RCT) and real world studies (RWS): Seamless design and implementation, with illustration of a large child abuse prevention study

Abstract:
Traditionally, randomized controlled trials (RCT) have been seen as the "gold standard" for evaluating the efficacy of interventions. However, mainly due to its inclusion and exclusion criteria, RCTs have well- known limitations of their generalizability to the general population in the real world setting. As a result, real-world studies (RWS) are gaining increasing interests in recent years, given their abilities of generating more realistic and generalizable results than traditional RCT, or even offering stronger evidence for efficiency of an intervention in a real world setting. And RWE has been increasingly valued by regulators and payers.

Even with conceptual distinctions, RCT and RWE can happily co-exist and complement each other. Here we report our efforts towards this direction.

Since 2014, we have successfully designed and implemented our iLookOut for Child Abuse project (iLookOut, https://ilookoutproject.org/), an online, interactive learning module about reporting suspected child maltreatment for early childhood care and education providers (CCPs). As designed, the iLookOut project has multiple phases, with Phase I as an RCT (ClinicalTrials.gov Identifier: NCT02225301), and Phase II as an RWS. In 2017, we published the Phase I (RCT) in 741 CCPs (https://journals.plos.org/plosone/article/authors?id=10.1371/journal.pone.0177777). And the Phase II, an RWS with 11,605 CCPs, is now in minor revision for publication. The RCT (Phase I) demonstrated that in a RCT setting, the iLookOut is efficient at improving CCPs' knowledge of and attitudes towards child maltreatment reporting. However, the generalizability of the RCT's results in a RWS setting remains unknown if we did not have an RWS. To address this question, we also designed and conducted the large RWS (Phase II) of the iLookOut. As hypothesized, we confirmed the replication of the earlier RCT findings, i.e., the iLookOut can improve CCPs' knowledge of and attitudes toward child maltreatment reporting in a real world setting. The large RWS (Phase II) yielded similar effect sizes for knowledge and attitudes as were found in the earlier smaller RCT (Phase I). Cohen's d for knowledge improvement was 0.95 in the RCT, 0.96 in the RWS; Cohen's d for attitude improvement was 0.98 in the RCT, 0.80 in the RWS.

In conclusion, although RCT and RWS are conceptually different, they should and can happily co- exist and complement each other by borrowing each other's strength and addressing each other's weakness. In addition, a seamless design connecting RCT and RWS is preferable, and the agreement on the results and conclusions between the RCT and RWS can offer stronger evidence for the validity and generalizability of the overall study, as illustrated by the findings from the RCT and the RWS of our iLookout for Child Abuse project. This seamless design and conduct of RCT and RWS within the same project can be a useful model for other interventional studies.

2019

Author: Gareth Sion Davies
Institution: University of Bristol
Title: Surgeons' lack of understanding of levels of evidence and trial methodology is a major barrier to randomized trials in surgery

Abstract:
Introduction: Randomized clinical trials (RCTs) provide the highest level of evidence to support practice, but RCTs in surgery may be challenging due to established methodological issues such as a lack of patient and surgeon equipoise. Breast reconstruction trials are particularly challenging for this reason and careful work is needed to identify potentially acceptable study designs. Implant-based breast reconstruction (IBBR), the most commonly performed breast reconstruction world-wide, has recently evolved with the introduction of new mesh-assisted techniques. These techniques have been widely adopted into practice without robust evidence and there is urgent need for high-quality

evidence to inform current practice.

iBRA is a four-phase study which aimed to inform the feasibility, design and conduct of an RCT of different approaches to implant-based breast reconstruction. In this aspect of the study, we used qualitative interviews to explore professionals' perceptions of future trials in IBBR, aiming to inform the design of a large-scale pragmatic RCT.

Methods: Semi-structured qualitative interviews were undertaken with a purposive sample of 33 surgeons involved in IBBR surgery to explore their attitudes to the feasibility of potential RCTs in IBBR. Interviews were transcribed verbatim and data was analyzed thematically using constant comparative techniques. Sampling, data collection and analysis were undertaken iteratively and concurrently until data saturation was achieved.

Results: Almost all surgeons acknowledged that the current practice of IBBR was based on limited evidence and highlighted the need for an increased evidence base to support practice. They recognized that RCTs provide the most robust scientific evidence but around half did not feel that trials were appropriate in IBBR or that they were needed to inform practice. Four key themes were identified to explain their lack of acceptance of RCTs. These included limited equipoise for different techniques despite an acknowledged lack of supporting evidence, the perceived difficulties of conducting RCTs particularly issues surrounding randomization and patient choice, underlying surgical dogma and decision-making guided by personal experience, and most notably a poor in-depth understanding of trial methodology. In
particular, this included minimal appreciation of levels of evidence with many surgeons suggesting that the same quality evidence could be derived from audit, observational, and non-randomized studies and a lack of understanding of pragmatic trial design with many stating that variation between centers would be a major barrier and limitation of RCTs in IBBR.

Conclusion: Surgeons' lack of understanding of pragmatic trials and limited appreciation of the importance of randomization in minimizing bias to provide the highest levels of evidence are major barriers to the successful conduct of RCTs in surgery. Interventions to educate surgeons about research methods may help to change the current surgical research culture, a change that is needed to improve evidence-based practice and to support surgeons to deliver future trials to benefit patients.

2018

Author: Andrea Viecelli
Institution: Princess Alexandra Hospital
Title: The Standardized Outcomes in Nephrology – Hemodialysis (SONG-HD) initiative: Establishing a core outcome set for trials in patients on hemodialysis

Abstract:
Introduction/objective: The Standardized Outcomes in Nephrology - Hemodialysis (SONG-HD) initiative aims to establish a core outcome set to be reported in all trials in hemodialysis based on the shared priorities of patients and health professionals.

Background: The prevalence of people with end-stage kidney disease in need of hemodialysis is steadily rising. Hemodialysis is a burdensome, time-consuming, and costly treatment that is associated with impaired quality of life and increased morbidity and mortality. In the past decade, more than 1500 reports of randomized trials in hemodialysis have been published, yet substantive improvements in patient outcomes remain to be seen. To some extent, this may be due to inconsistent and selective reporting of highly variable outcomes that are often of limited importance to patients and clinicians which limits the reliability and comparability of outcomes across trials for shared decision-making.

Methods: SONG-HD used an evidence-based consensus process. The five phases to establish core outcome domains included: a systematic review of outcomes reported in trials in hemodialysis; focus groups with nominal group technique

with patients and caregivers to identify and prioritize outcomes, and describe reasons for their choices; multi-stakeholder interviews to elicit individual values and perspectives on outcomes; an international three-round online Delphi survey with patients, caregivers and health professionals (i.e. clinicians, nurses, allied health professionals, researchers, policy makers, and other relevant stakeholders with expertise in hemodialysis) to achieve consensus on critically important outcomes; and a consensus workshop to establish the core outcome set. The phases to establish the core outcome measures for each core outcome domain included: a systematic review of outcome measures reported in clinical trials; an international multi-stakeholder survey to rate and rank selected outcomes
using a 9-point Likert scale and Best Worst Scale; consensus workshops to discuss measurement properties and feasibility aspects; and pilot and validation studies to evaluate and validate the identified core outcome measures.

Results: In total, 1376 patients, caregivers and health professionals from 73 countries participated in the consensus process to identify the four core outcome domains for hemodialysis: fatigue, vascular access, cardiovascular disease, and mortality. For fatigue, the impact of fatigue on life participation was the most critically important dimension and a 3-item questionnaire to assess fatigue is currently being validated. For vascular access, the function of a hemodialysis access was considered of most critical importance and defined as the need for an intervention/procedure to maintain the use of the vascular access for hemodialysis. For cardiovascular disease, myocardial infarction and sudden cardiac death were identified as the most critically important outcomes. Pilot and validation studies are in progress to ensure that the core outcome measures are feasible and robust.

Conclusions: Consistent reporting of the core outcome set – fatigue, vascular access function, myocardial infarction, sudden cardiac death, and all-cause mortality – as a minimum in all trials in hemodialysis will improve the integrity, comparability, usability, and potential impact of trial-based evidence to inform decision-making in hemodialysis. This may ultimately lead to improved outcomes that are meaningful and important to patients and their clinicians.

2017

Author: Lawrence P Richer
Institution: University of Alberta
Title: Placebo response is not decreases by enrichment trial designs in randomized controlled trials of triptan medications in the paediatric age group

Abstract:
Objectives: To assess the effect of enrichment on the placebo response rate in randomized controlled trials of triptan medications in the pediatric age group.

Background: Numerous triptan medications approved for use in adults have failed to demonstrate efficacy in children or adolescents and the high placebo response rate is often implicated. More recent studies have used enrichment designs in which participants who respond to placebo in the early, single-blind, run- in phase are not randomized to the double-blind phase. A systematic review of clinical trials for triptan medications was conducted to evaluate and compare the placebo response rate.

Methods: We searched seven bibliographic databases and four clinical trial registers as well as gray literature for studies through February 2016. We included prospective randomized controlled clinical trials of children and adolescents with migraine, comparing acute symptom relieving migraine medications with placebo in the ambulatory setting and 15811 records were screened. Pain-free and headache relief at 2 hours were the primary efficacy outcome measures. The proportion of placebo responders and standard error were calculated for each study and data entered into RevMan 5.3 (Cochrane Collaboration) for analysis. Meta-analysis, forest plots, and tests for sub-group differences were calculated using generic inverse variance as the statistical method and the random effects analysis model.

Results: We identified 26 randomized controlled trials (RCTs) of migraine symptom-relieving medications in adolescents and children. The placebo response rate overall for all 23 triptan studies in adolescents was 21% (95% CI 18-24) for pain-

free status and 48% (95% CI 44-53; 21 studies) for headache relief. The placebo response rate in adolescents did not significantly decrease (p=0.08) with the enrichment design studies at 17% (95% CI 11-22; 4 studies; I2=77%) and non-enriched designs at 22% (95% CI 19-26; 19
studies; I2=65%) for pain-free status and 49% (95% CI 38-61; 3 studies, I2=83%) and 48% (95% CI 42-54; 19 studies; I2=84%) respectively for headache relief. There was significant heterogeneity between studies. Subgroup and sensitivity analysis comparing cross-over design vs parallel group; inclusion of only parallel group designs; route od delivery; and age did not explain the observed heterogeneity.

Conclusions: Enrichment designs did not significantly decrease the placebo response rate in randomized controlled trials of triptan medications in the pediatric age group. High between study variation was observed suggesting mechanisms other than those explored in this study may affect placebo response.