Sylvan Green Award Winners

2021

Author: Lara Philipps
Institute: 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
Institute: 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
Institute: 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
Institute: 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
Institute: 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.