Factors affecting patient recruitment into cancer trials

Nearly one in four publicly sponsored cancer clinical trials fails to enrol enough participants to draw valid conclusions about treatments or techniques.

Bennette et al (2015) found a number of measurable trial characteristics that were associated with poor accrual to NCTN trials, such as increased competition for patients from currently ongoing trials, planning to enrol a higher proportion of the available patient population, and not evaluating a new investigational agent or targeted therapy.

Bennette CS, Ramsey SD, McDermott CL, Carlson JJ, Basu A, Veenstra DL (2015) Predicting low accrual in the National Cancer Institute's Cooperative Group Clinical Trials. *J Natl Cancer Inst* (doi: 10.1093/jnci/djv324)

Anti-rheumatic drugs in pregnancy and breastfeeding

New guidelines from the British Society for Rheumatology (Flint et al, 2016) make recommendations for use of standard and/or biologic disease-modifying anti-rheumatic drugs in women who are pregnant or breastfeeding, providing crucial advice for clinicians, obstetricians and midwives.

Commenting on the guidelines, lead author Dr Ian Giles, Professor at the Centre for Rheumatology Research, UCL Division of Medicine, said: 'I hope this approach will allow adequate control of inflammatory rheumatic disease activity and prevent the unnecessary withdrawal of disease-ameliorating anti-rheumatic therapies which have not been shown to be harmful in pregnancy and breastfeeding.'

Flint J, Panchal S, Hurrell A et al; BSR and BHPR Standards, Guidelines and Audit Working Group (2016) BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology (Oxford)* (doi: 10.1093/rheumatology/kev404)

Breast cancer detection rate using ultrasound is comparable to that using mammography

Mammography is not widely available in all countries, and the incidence of breast cancer is increasing. A study was undertaken to consider the performance characteristics using ultrasound instead of mammography to screen for breast cancer (Berg et al, 2015).

A total of 2809 participants were enrolled at 20 sites in the United States, Canada, and Argentina, of whom 2662 participants completed three annual screens (7473 examinations) with ultrasound and film-screen (n = 4351) or digital (n = 3122) mammography and had biopsy or 12-month follow-up. Cancer detection, recall and positive predictive values were determined. All statistical tests were two-sided.

The results showed that 110 women had 111 breast cancer events, 89 (80.2%) of which were invasive cancers (median size 12 mm). The number of ultrasound screens to detect one cancer was 129 (95% confidence interval = 110–156), and for mammography was 127 (95% confidence interval = 109–152).

Cancer detection was comparable for ultrasound and mammography at 58 of 111 (52.3%) *vs* 59 of 111 (53.2%, P=0.90), with ultrasound-detected cancers more likely to be invasive (53/58, 91.4%, median size 12 mm, range = 2–40 mm), *vs* mammography at 41 of 59 (69.5%, median size 13 mm, range = 1–55 mm, P<0.001). Invasive cancers detected by ultrasound were more frequently node-negative (34 of 53; 64.2%), compared to 18 of 41 (43.9%) detected by mammography (P=0.003).

For 4814 incidence screens (years 2 and 3), ultrasound had higher recall and biopsy rates and lower positive predictive value of biopsy than mammography. The recall rate was 10.7% (n = 515) *vs* 9.4% (n = 453, P=0.03), the biopsy rate was 5.5% (n = 266) *vs* 2.0% (n = 97, P<0.001), and positive predictive value was 11.7% (31/266) *vs* 38.1% (37/97, P<0.001).

The cancer detection rate with ultrasound is comparable to that with mammography, with a greater proportion of invasive and node-negative cancers among ultrasound detections. False positives are more common with ultrasound screening.

The authors stated: 'Where mammography is available, ultrasound should be seen as a supplemental test for women with dense breasts who do not meet high-risk criteria for screening magnetic resonance imaging and for high-risk women with dense breasts who are unable to tolerate magnetic resonance imaging.'

Commenting on the findings, lead author Professor Wendie Berg, Professor of Radiology in the Magee-Womens Hospital of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, highlighted: 'We have long known that ultrasound is very good at seeing masses that we do not see on mammography, for example palpable cysts or cancers. Because ultrasound is not limited by tissue density, it sees many masses that are not seen on mammography, but it is important to remember that most of those masses are not cancer.'

Professor Berg concluded: 'Where mammography is already widespread, using ultrasound in addition will help find more cancers. It is time that we routinely offer this to women with dense breasts as a choice. Where mammography is not available, ultrasound certainly warrants further evaluation.'

Professor Wendie Berg, Professor of Radiology, Magee-Womens Hospital of UPMC, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Berg WA, Bandos AI, Mendelson EB, Lehrer D, Jong RA, Pisano ED (2015) Ultrasound as the primary screening test for breast cancer: analysis from ACRIN 6666. *J Natl Cancer Inst* (doi: 10.1093/jnci/djv367)

Association between social media use and sleep disturbances in young adults

Young adults who spend a lot of time on social media during the day or check it frequently throughout the week are more likely to suffer sleep disturbances than their peers who use social media less, according to new research (Levenson et al, 2016).

The study, supported by the National Institutes of Health, indicates that physicians should consider asking young adult patients about their social media habits when assessing sleep issues.

'This is one of the first pieces of evidence that social media use really can impact your sleep,' said lead author Dr Jessica C Levenson, a postdoctoral researcher in the Department of Psychiatry, University of Pittsburgh School of Medicine. 'And it uniquely examines the association between social media use and sleep among young adults who are, arguably, the first generation to grow up with social media.'

Dr Levenson and her colleagues sampled 1788 American adults aged 19–32 years, using questionnaires to determine social media use and an established measurement system to assess sleep disturbances. The questionnaires asked about the 11 most popular social media platforms at the time: Facebook, YouTube, Twitter, Google Plus, Instagram, Snapchat, Reddit, Tumblr, Pinterest, Vine and LinkedIn.

On average, the participants used social media a total of 61 minutes per day and visited various social media accounts 30 times per week. The assessment showed that nearly 30% of the participants had high levels of sleep disturbance.

The participants who reported most frequently checking social media throughout the week had three times the likelihood of sleep disturbances compared with those who checked least frequently. Participants who spent the most total time on social media throughout the day had twice the risk of sleep disturbance as their peers who spent less time on social media.

'This may indicate that frequency of social media visits is a better predictor of sleep difficulty than overall time spent on social media,' Dr Levenson explained. 'If this is the case, then interventions that counter obsessive "checking" behaviour may be most effective.'

Senior author Dr Brian A Primack, assistant vice chancellor for health and society in Pitt's Schools of the Health Sciences, emphasized that more study is needed, particularly to determine whether social media use contributes to sleep disturbance, whether sleep disturbance contributes to social media use – or both.

Levenson JC, Shensa A, Sidani JE, Colditz JB, Primack BA (2016) The association between social media use and sleep disturbance among young adults. *Prev Med* (doi: 10.1016/j.ypmed.2016.01.001)

Blood test can predict the absence of pre-eclampsia in women in whom it is clinically suspected

Proteinuria and elevated blood pressure are diagnostic criteria for pre-eclampsia, but the clinical presentation is variable. There is a need for a reliable predictor of pre-eclampsia (particularly its absence) in the short term in women with suspected pre-eclampsia.

PROGNOSIS (Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study) was a prospective, multicentre, observational study designed to investigate the value of using the ratio of soluble fms-like tyrosine kinase 1 to placental growth factor (sFlt-1:PlGF) to predict the presence or absence of pre-eclampsia in the short term.

The analysis included 1050 eligible participants at 30 sites. Age, gestational age, body mass index before pregnancy, and smoking status did not differ significantly between participants in whom pre-eclampsia developed and those in whom it did not. The results (Zeisler et al, 2016) showed that an sFlt-1:PlGF ratio of 38 or lower can be used to predict the short-term absence of pre-eclampsia in women in whom the syndrome is suspected clinically.

Zeisler H, Llurba E, Chantraine F et al (2016) Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. *N Engl J Med* **374**(1): 13–22 (doi: 10.1056/NEJMoa1414838)

First clinical guidelines for chronic pulmonary aspergillosis

The world's first guidelines for chronic pulmonary aspergillosis, detailing the features and giving treatment recommendations, have been published (doi: 10.1183/13993003.00583-2015). Chronic pulmonary aspergillosis kills about 80% of sufferers over 5 years, unless diagnosed and treated with long-term antifungals. Across Europe, an estimated 240 000 people have chronic pulmonary aspergillosis.

Breakthrough discovery in the genetics of corneal dystrophies

Researchers have discovered a new genetic cause of corneal dystrophy. This paves the way for further studies to understand the biological processes leading to corneal dystrophy and to develop new treatments, with the future hope of replacing the need for corneal transplants in these patients (doi: 10.1016/j.ajhg.2015.11.018).

Frailty may increase risk of complications following urological surgery

Among 95 108 patients undergoing 21 different urological procedures, such as bladder or prostate removal, the average frequency of complications per individual was 11.7%. Patients who were frail were 1.7 times more likely to experience complications after surgery (doi: 10.1111/bju.13399).

Taking paroxetine in early pregnancy linked to increased risk of birth defects

To provide a comprehensive assessment of the effects of paroxetine on newborns, a team led by Professor Anick Bérard of CHU Sainte-Justine and the University of Montreal conducted a literature review and meta-analysis of all relevant studies published from 1966 to 2015 (Bérard et al, 2016). The investigators uncovered 23 eligible studies.

Compared with no use of paroxetine, first trimester use of paroxetine was associated with a 23% increased risk of any major congenital malformations and a 28% increased risk of major cardiac malformations in newborns. The baseline risk of major malformations is 3% and of cardiac malformations is 1%; however, any increase in risk is significant, especially when considering that the benefit of using selective serotonin-reuptake inhibitors during pregnancy – when changes in metabolism cause the drugs to be cleared from the body at a faster rate – is debatable.

Bérard A, Iessa N, Chaabane S, Muanda FT, Boukhris T, Zhao J-P (2016) The risk of major cardiac malformations associated with paroxetine use during the first trimester of pregnancy: a systematic review and meta-analysis. *Br J Clin Pharmacol* (doi: 10.1111/bcp.12849)

Adding opicapone 50 mg to levodopa could simplify treatment for patients with Parkinson's disease

Opicapone is a novel, once-daily, potent third-generation catechol-O-methyltransferase inhibitor. A randomized, double-blind, placebo-controlled and active-controlled trial of opicapone as an adjunct to levodopa was undertaken in patients with Parkinson's disease with end-of-dose motor fluctuations (Ferreira et al, 2015).

Patients aged 30–83 years were enrolled at 106 specialist centres across 19 European countries and Russia and were randomly assigned to oral treatment with opicapone (5 mg, 25 mg or 50 mg once daily), placebo, or entacapone (200 mg with every levodopa intake) for 14–15 weeks.

The primary endpoint was the change from baseline to end of study treatment in absolute time in the off state, as assessed by daily paper patient diaries.

Between 31 March 2011 and 30 November 2013, 600 were randomly assigned. Of these 590 patients were included in the full analysis set and 537 in the per-protocol set. The mean change in time in the off state was -56·0 minutes for placebo, -96·3 minutes for entacapone, -91·3 minutes for opicapone 5 mg, -85·9 minutes for opicapone 25 mg, and -116·8 minutes for opicapone 50 mg. Treatment with opicapone 50 mg was superior to placebo and non-inferior to entacapone. Treatment with opicapone 5 mg (P=0·056) or 25 mg (P=0·080) was not significantly different from treatment with placebo.

The most common adverse events were dyskinesia, insomnia and constipation. Serious adverse events were reported in six patients in the placebo group, eight in the entacapone group, four each in the opicapone 5 mg and opicapone 50 mg groups, and one in the opicapone 25 mg group.

The authors concluded that adding opicapone 50 mg to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations could enable a simplified drug regimen that allows physicians to individually tailor the existing levodopa daily regimen, by potentially reducing the total daily levodopa dose, increasing the dosing interval, and ultimately reducing the number of intakes, thereby maximizing its benefit.

Commenting on the findings, Professor Patrício Soares da Silva, Department of Research and Development, BIAL, S Mamede do Coronado, Portugal, said: 'This study has several important strengths: the proportion of patients remaining in the study and completing treatment was high and the study incorporated both a placebo group and entacapone, which is commonly used in the management of end-of-dose motor fluctuations, as an active comparator arm.'

Ferreira JJ, Lees A, Rocha JF, Poewe W, Rascol O, Soares-da-Silva P; Bi-Park 1 investigators (2015) Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. *Lancet Neurol* (doi: 10.1016/S1474-4422(15)00336-1)

Exercise to improve skill and coordination can help reduce lower back pain

A new Cochrane review (Saragiotto et al, 2016) shows that targeting exercises to muscles that support and control the spine offers another strategy to reduce pain and disability caused by lower back pain.

Motor control exercise is a popular form of exercise that aims to improve coordination of the muscles that control and support the spine. Patients are initially guided by a therapist to practise normal use of the muscles with simple tasks. As the patient's skill increases the exercises become more complex and include the functional tasks that the person needs to perform during work and/or leisure activities.

The study gathered together data from 29 randomized trials involving a total of 2431 men and women, aged between 22 and 55 years old. The trials investigated the impact of using motor control exercises as a treatment for lower back pain compared with other forms of exercise or doing nothing.

The Cochrane authors found that people who used motor control exercises experienced improvements, especially in pain and disability, compared with minimal intervention. When compared with other types of exercise at intervals between 3 and 12 months motor control exercise provided similar results for pain and disability.

Lead author, physiotherapist Bruno Saragiotto, from The George Institute, University of Sydney, Australia, said: 'At present, we don't really know how motor control exercise compares with other forms of exercise in the long term. It's important we see more research in this field so that patients can make more informed choices about persisting with treatment.'

Saragiotto BT, Maher CG, Yamato TP et al (2016) Motor control exercise for chronic non-specific low-back pain. *Cochrane Database Syst Rev* **1**: CD012004 (doi: 10.1002/14651858.CD012004)

Atrial fibrillation is a stronger risk factor for cardiovascular disease and death in women than men

A meta-analysis by an international team of researchers (Emdin et al, 2016) has analysed the results of 30 studies, published between January 1966 and March 2015, involving over 4 million participants. These studies reported sex-specific associations between atrial fibrillation and all-cause mortality, cardiovascular mortality, stroke, cardiac events (cardiac death and non-fatal myocardial infarction), and heart failure.

The team found that atrial fibrillation was associated with a 12% higher relative risk of all-cause mortality in women and a significantly stronger risk of stroke, cardiovascular mortality, cardiac events and heart failure. Results were broadly consistent after further sensitivity analyses. It is unclear what could cause these differences between women and men.

The authors believe that these results support the development of a specific risk score for atrial fibrillation in women, as recently recommended by the American Heart Association. They added that estimation of the global and regional burden of atrial fibrillation should be independent of sex, while 'allocation of public health resources for prevention and treatment of atrial fibrillation should also consider the differential effects of atrial fibrillation by sex.'

Lead author Dr Connor Emdin, of the George Institute for Global Health, University of Oxford, Oxford, said: 'This study shows that atrial fibrillation affects women more strongly than men and suggests that women with atrial fibrillation should be treated aggressively and that clinicians should use risk scores that contain female sex (e.g. CHA2DS2-VASC).'

Dr Connor Emdin, George Institute for Global Health, University of Oxford, Oxford

Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA (2016) Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* **352**: h7013 (doi: 10.1136/bmj.h7013)

Long-term ozone exposure increases risk of acute respiratory disease syndrome in critically ill patients

Critically ill patients who are exposed to higher daily levels of ozone are more likely to develop acute respiratory disease syndrome, according to a new study (Ware et al, 2015). While previous research has shown a clear association between cigarette smoke and acute respiratory disease syndrome, this study is the first to demonstrate a risk related to ozone.

The researchers analysed exposure using a heterogenous group of 1558 critically ill patients from the Validating Acute Lung Injury Biomarkers for Diagnosis cohort. They found that as long-term ozone exposure increased, so did rates of acute respiratory disease syndrome, which developed in 563 patients. The association between acute respiratory disease syndrome risk and ozone exposure was greatest among trauma patients (n=552). In addition, 'ozone was significantly associated with acute respiratory disease syndrome only in current smokers and not in non-smokers,' wrote the researchers.

As the potentially harmful health consequences of ozone exposure continue to draw more concern, there may be a need for a more strict ozone standard.

Ware LB, Zhao Z, Koyama T et al (2015) Long-term ozone exposure increases the risk of developing the acute respiratory distress syndrome. *Am J Respir Crit Care Med* (doi: 10.1164/rccm.201507-1418OC)

Long-term effects of retinoblastoma

Limited data are available regarding long-term morbidity in adult survivors of retinoblastoma. The Retinoblastoma Survivor Study is a retrospective cohort of adult survivors of retinoblastoma diagnosed between 1932 and 1994. Participants completed a comprehensive questionnaire adapted from the Childhood Cancer Survivor Study surveys.

Multivariate Poisson regression was used to compare survivors of retinoblastoma with 2377 non-retinoblastoma controls, consisting of the Childhood Cancer Survivor Study sibling cohort and survivors with bilateral *vs* unilateral disease.

Survivors of retinoblastoma (53.6% with bilateral disease) and non-retinoblastoma controls had a mean age of 43.3 years (standard deviation = 11 years) and 37.6 years (standard deviation = 8.6 years) respectively at the time of study enrolment. At a median follow-up of 42 years (range, 15–75 years), 86.6% of survivors of retinoblastoma had at least one condition and 71.1% had a severe or life-threatening condition.

The adjusted relative risk of a chronic condition in survivors compared with non-retinoblastoma controls was 1.4 (P<0.01), and for a severe or life-threatening condition was 7.6 (P<0.01).

Survivors of retinoblastoma have an increased risk of chronic conditions compared with non-retinoblastoma controls. After excluding ocular conditions and second malignant neoplasms, this excess risk was found to persist only for those with bilateral disease.

Lead author, Dr Danielle Novetsky Friedman, of Memorial Sloan Kettering Cancer Center in New York City, said: 'Appropriate lifelong risk-based screening of this population will allow for timely treatment of any medical problems that may arise.'

Friedman DN, Chou JF, Oeffinger KC et al (2016), Chronic medical conditions in adult survivors of retinoblastoma: Results of the Retinoblastoma Survivor Study. *Cancer* (doi: 10.1002/cncr.29704)