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Abstracts' Service

Compliance with Results Reporting at ClinicalTrials.gov

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Background. The Food and Drug Administration Amendments Act (FDAAA) mandates timely reporting of results of applicable clinical trials to ClinicalTrials.gov. We characterized the proportion of applicable clinical trials with publicly available results and determined independent factors associated with the reporting of results.

Methods. Using an algorithm based on input from the National Library of Medicine, we identified trials that were likely to be subject to FDAAA provisions (highly likely applicable clinical trials, or HLACTs) from 2008 through 2013. We determined the proportion of HLACTs that reported results within the 12-month interval mandated by the FDAAA or at any time during the 5-year study period. We used regression models to examine characteristics associated with reporting at 12 months and throughout the 5-year study period.

Results. From all the trials at ClinicalTrials.gov, we identified 13,327 HLACTs that were terminated or completed from January 1, 2008, through August 31, 2012. Of these trials, 77.4% were classified as drug trials. A total of 36.9% of the trials were phase 2 studies, and 23.4% were phase 3 studies; 65.6% were funded by industry. Only 13.4% of trials reported summary results within 12 months after trial completion, whereas 38.3% reported results at any time up to September 27, 2013. Timely reporting was independently associated with factors such as FDA oversight, a later trial phase, and industry funding. A sample review suggested that 45% of industry-funded trials were not required to report results, as compared with 6% of trials funded by the National Institutes of Health (NIH) and 9% of trials that were funded by other government or academic institutions.

Conclusions. Despite ethical and legal obligations to disclose findings promptly, most HLACTs did not report results to ClinicalTrials.gov in a timely fashion during the study period. Industry-funded trials adhered to legal obligations more often than did trials funded by the NIH or other government or academic institutions. (Funded by the Clinical Trials Transformation Initiative and the NIH.)

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

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Background. Mechanical-ventilation strategies that use lower end-inspiratory (plateau) airway pressures, lower tidal volumes (V_T), and higher positive end-expiratory pressures (PEEPs) can improve survival in patients with the acute respiratory distress syndrome (ARDS), but the relative importance of each of these components is uncertain. Because respiratory-system compliance (C_{RS}) is strongly related to the volume of aerated remaining functional lung during disease (termed functional lung size), we hypothesized that driving pressure ($\Delta P = V_T / C_{RS}$), in which V_T is intrinsically normalized to functional lung size (instead of predicted lung size in healthy persons), would be an index more strongly associated with survival than V_T or PEEP in patients who are not actively breathing.

Methods. Using a statistical tool known as multilevel mediation analysis to analyze individual data from 3562 patients with ARDS enrolled in nine previously reported randomized trials, we examined ΔP as an independent variable associated with survival. In the mediation analysis, we estimated the isolated effects of changes in ΔP resulting from randomized ventilator settings while minimizing confounding due to the baseline severity of lung disease.

Results. Among ventilation variables, ΔP was most strongly associated with survival. A 1-SD increment in ΔP (approximately 7 cm of water) was associated with increased mortality (relative risk, 1.41; 95% confidence interval [CI], 1.31 to 1.51; P<0.001), even in patients receiving "protective" plateau pressures and VT (relative risk, 1.36; 95% CI, 1.17 to 1.58; P<0.001). Individual changes in V_T or PEEP after randomization were not independently associated with survival; they were associated only if they were among the changes

that led to reductions in ΔP (mediation effects of ΔP, P=0.004 and P=0.001, respectively).

Conclusions. We found that ΔP was the ventilation variable that best stratified risk. Decreases in ΔP owing to changes in ventilator settings were strongly associated with increased survival. (Funded by Fundação de Amparo e Pesquisa do Estado de São Paulo and others.).

Emphysematous Phenotype is an Independent Predictor for Frequent Exacerbation of COPD

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Setting. Frequent exacerbation is an important phenotype in chronic obstructive pulmonary disease (COPD), while emphysema is associated with many comorbidities and lung function decline.

Objective. To investigate unique features of frequent exacerbators and test the hypothesis that emphysematous phenotype is associated with frequent exacerbations of COPD.

Methods. A total of 380 COPD patients were recruited from 16 hospitals in Korea from June 2005 to April 2012 for analysis. We searched for independent predictors of frequent exacerbators in comparison with non-exacerbators.

Results. As the severity of emphysema increased, forced expiratory volume in 1 s (FEV_1), and FEV_1/FVC (forced volume capacity) worsened; hyperinflationary features characterised by higher total lung capacity (TLC) were observed ($P < 0.05$). Frequent exacerbators had lower body mass index (BMI), higher St George's Respiratory Questionnaire (SGRQ) scores, higher residual volume (RV)/TLC, more severe airflow limitation (lower FEV_1 and FEV_1/FVC), lower carbon monoxide diffusion capacity, lower serum protein levels and a higher emphysema index than non-exacerbators ($P < 0.05$). In multivariate analysis, frequent exacerbators were independently associated with a higher emphysema index, lower serum protein levels and higher RV/TLC ($P < 0.05$).

Conclusion. Our data show that the severity of emphysema, severe static hyperinflation and serum lower protein levels are independent predictors of frequent exacerbations in COPD patients.

Internet-based Intervention for Smoking Cessation (StopAdvisor) in People with Low and High Socioeconomic Status: A Randomised Controlled Trial

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Background. Internet-based interventions for smoking cessation could help millions of people stop smoking at very low unit costs; however, long-term biochemically verified evidence is scarce and such interventions might be less effective for smokers with low socioeconomic status than for those with high status because of lower online literacy to engage with websites. We aimed to assess a new interactive internet-based intervention (StopAdvisor) for smoking cessation that was designed with particular attention directed to people with low socioeconomic status.

Methods. We did this online randomised controlled trial between Dec 6, 2011, and Oct 11, 2013, in the UK. Participants aged 18 years and older who smoked every day were randomly assigned (1:1) to receive treatment with StopAdvisor or an information-only website. Randomisation was automated with an unseen random number function embedded in the website to establish which treatment was revealed after the online baseline assessment. Recruitment continued until the required sample size had been achieved from both high and low socioeconomic status subpopulations. Participants, and researchers who obtained data and did laboratory analyses, were masked to treatment allocation. The primary outcome was 6 month sustained, biochemically verified abstinence. The main secondary outcome was 6 month, 7 day biochemically verified point prevalence. Analysis was by intention to treat. Homogeneity of intervention effect across the socioeconomic subsamples was first assessed to establish whether overall or separate subsample analyses were appropriate. The study is registered as an International Standard Randomised Controlled Trial, number ISRCTN99820519.

Findings. We randomly assigned 4613 participants to the StopAdvisor group (n=2321) or the control group

(n=2292); 2142 participants were of low socioeconomic status and 2471 participants were of high status. The overall rate of smoking cessation was similar between participants in the StopAdvisor and control groups for the primary (237 [10%] *vs* 220 [10%] participants; relative risk [RR] 1·06, 95% CI 0·89–1·27; p=0·49) and the secondary (358 [15%] *vs* 332 [15%] participants; 1·06, 0·93–1·22; p=0·37) outcomes; however, the intervention effect differed across socioeconomic status subsamples (1·44, 0·99–2·09; p=0·0562 and 1·37, 1·02–1·84; p=0·0360, respectively). StopAdvisor helped participants with low socioeconomic status stop smoking compared with the information-only website (primary outcome: 90 [8%] of 1088 *vs* 64 [6%] of 1054 participants; RR 1·36, 95% CI 1·00–1·86; p=0·0499; secondary outcome: 136 [13%] *vs* 100 [10%] participants; 1·32, 1·03–1·68, p=0·0267), but did not improve cessation rates in those with high socioeconomic status (147 [12%] of 1233 *vs* 156 [13%] of 1238 participants; 0·95, 0·77–1·17; p=0·61 and 222 [18%] *vs* 232 [19%] participants; 0·96, 0·81–1·13, p=0·64, respectively).

Interpretation. StopAdvisor was more effective than an information-only website in smokers of low, but not high, socioeconomic status. StopAdvisor could be implemented easily and made freely available, which would probably improve the success rates of smokers with low socioeconomic status who are seeking online support.

The Effect of Long-term Macrolide Treatment on Respiratory Microbiota Composition in Non-cystic Fibrosis Bronchiectasis: An Analysis from the Randomised, Double-blind, Placebo-controlled BLESS Trial

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Background. Long-term macrolide treatment has proven benefit in inflammatory airways diseases, but whether it leads to changes in the composition of respiratory microbiota is unknown. We aimed to assess whether long-term, low-dose erythromycin treatment changes the composition of respiratory microbiota in people with non-cystic fibrosis bronchiectasis.

Methods. Microbiota composition was determined by 16S rRNA gene sequencing of sputum samples from participants in the BLESS trial, a 12-month, double-blind, placebo-controlled trial of twice-daily erythromycin ethylsuccinate (400 mg) in adult patients with non-cystic fibrosis bronchiectasis and at least two infective exacerbations in the preceding year. The primary outcome was within-patient change in respiratory microbiota composition (assessed by Bray-Curtis index) between baseline and week 48, comparing erythromycin with placebo. The BLESS trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12608000460303.

Findings. The BLESS trial took place between Oct 15, 2008, and Dec 14, 2011. Paired sputum samples were available from 86 randomly assigned patients, 42 in the placebo group and 44 in the erythromycin group. The change in microbiota composition between baseline and week 48 was significantly greater with erythromycin than with placebo (median Bray-Curtis score 0·52 [IQR 0·14-0·78] *vs* 0·68 [0·46-0·93]; median difference 0·16, 95% CI 0·01-0·33; p=0·03). In patients with baseline airway infection dominated by Pseudomonas aeruginosa, erythromycin did not change microbiota composition significantly. In those with infection dominated by organisms other than P. aeruginosa, erythromycin caused a significant change in microbiota composition (p=0·03 [by analysis of similarity]), representing a reduced relative abundance of Haemophilus influenzae (35·3% [5·5-91·6] *vs* 6·7% [0·8-74·8]; median difference 12·6%, 95% CI 0·4-28·3; p=0·04; interaction p=0·02) and an increased relative abundance of P.aeruginosa (0·02% [0·00-0·33] *vs* 0·13% [0·01-39·58]; median difference 6·6%, 95% CI 0·1-37·1; p=0·002; interaction p=0·45). Compared with placebo, erythromycin reduced the rate of pulmonary exacerbations over the 48 weeks of the study in patients with P. aeruginosa-dominated infection (median 1 [IQR 0-3] *vs* 3 [2-5]; median difference -2, 95% CI -4 to -1; p=0·01), but not in those without P. aeruginosa-dominated infection (1 [0-2] *vs* 1 [0-3]; median difference 0, -1 to 0; p=0·41; interaction p=0·04).

Interpretation. Long-term erythromycin treatment changes the composition of respiratory microbiota in patients with bronchiectasis. In patients without P. aeruginosa airway infection, erythromycin did not significantly reduce exacerbations and promoted displacement of H. influenzae by more macrolide-tolerant pathogens including P. aeruginosa. These findings argue for a cautious approach to chronic macrolide use in patients without P. aeruginosa airway infection.

Inappropriate Care in European ICUs: Confronting Views From Nurses and Junior and Senior Physicians

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Background. ICU care providers often feel that the care given to a patient may be inconsistent with their professional knowledge or beliefs. This study aimed to assess differences in, and reasons for, perceived inappropriate care (PIC) across ICU care providers with varying levels of decision-making power.

Methods. We present subsequent analysis from the Appropricus Study, a cross-sectional study conducted on May 11, 2010, which included 1,218 nurses and 180 junior and 227 senior physicians in 82 European adult ICUs. The study was designed to evaluate PIC. The current study focuses on differences across health-care providers regarding the reasons for PIC in real patient situations.

Results. By multivariate analysis, nurses were found to have higher PIC rates compared with senior and junior physicians. However, nurses and senior physicians were more distressed by perceived disproportionate care than were junior physicians (33%, 25%, and 9%, respectively; P = .026). A perceived mismatch between level of care and prognosis (mostly excessive care) was the most common cause of PIC. The main reasons for PIC were prognostic uncertainty among physicians, poor team and family communication, the fact that no one was taking the initiative to challenge the inappropriateness of care, and financial incentives to provide excessive care among nurses. Senior physicians, compared with nurses and junior physicians, more frequently reported pressure from the referring physician as a reason. Family-related factors were reported by similar proportions of participants in the three groups.

Conclusions. ICU care providers agree that excessive care is a true issue in the ICU. However, they differ in the reasons for the PIC, reflecting the roles each caregiver has in the ICU. Nurses charge physicians with a lack of initiative and poor communication, whereas physicians more often ascribe prognostic uncertainty. Teaching ICU physicians to deal with prognostic uncertainty in more adequate ways and to promote ethical discussions in their teams may be pivotal to improving moral distress and the quality of patient care.