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Journal of Cystic Fibrosis xx (2014) xxx – xxx

Journal of Cystic Fibrosis

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Editorial

At last, *Burkholderia spp*. is one of the inclusion criteria — A negative (but published) randomised controlled trial

This edition of the Journal of Cystic Fibrosis sees the publication of the negative results from the multicentre study of nebulised aztreonam in CF patients with chronic *Burkholderia* infection [1]; what is unusual about this?

On 3rd January 2014, in the UK, the House of Commons Committee of Public Accounts published a report on access to clinical trial information, specifically relating to influenza therapy [2]. In their summary they stated "…important information about clinical trials is routinely and legally withheld from doctors and researchers by manufacturers. This longstanding regulatory and cultural failure impacts on all of medicine, and undermines the ability of clinicians, researchers and patients to make informed decisions about which treatment is best". As long ago as 1986, Professor RJ Simes pointed out that published clinical trial literature may be biased in favour of positive or promising results [3]. Giving evidence to the Parliamentary Committee, Dr Ben Goldacre said that a National Institute for Health Research (NIHR) review in 2010 estimated that the chance of completed trials being published is about half, but that trials with positive results were about twice as likely to be published compared to negative ones [2]. This has been backed up by a Cochrane systematic review, which concluded that trials with positive findings (defined as statistically significant, or a positive direction of treatment effect, or results perceived as being 'important or striking') had nearly four times (with 95% confidence interval 2.7–5.7) the odds of being published compared to negative trials [4]. Assuming a strong hypothesis, an important question, robust methodology with adequate recruitment to satisfy power calculations, a study should always be publishable, even if the results are negative.

In theory, trial registries should improve this situation. From 2005 the International Committee of Medical Journal Editors (ICMJE) mandated that a trial needed to have been registered in a clinical trials registry for it to be considered for later publication [5]. This should at least alert researchers that a trial is being carried out and results should be expected, although inevitably it is the presentation at a conference or the actual publication that brings the results to the attention of the medical community. However a study in 2011 showed that only 1 in 5 trials registered on ClinicalTrials.gov (that anyway were subject to mandatory reporting due to FDA legislation), had been reported within 1 year of the completion of the trial [6]. Of course some may have been published after that, but there is a delay in publication of studies with negative results compared to positive ones, which a Cochrane review showed was about 1 year [7,8]. Recent legislation has been agreed by the European Parliament (EU Clinical Trials Directive) that ensures all clinical trials are registered, and once completed, are made publicly available. The European ombudsman has stated that there is no 'commercially confidential information' in clinical trial protocols or reports, and that the interests of public health and the citizens' right to know should overcome any claim by drug companies that commercial confidentiality should allow trial results to be withheld. However Peter Gøtzsche, director of the Nordic Cochrane Centre, does not believe the new legislation goes far enough [9].

Are editors of journals biased towards positive studies? Whilst one would like to think this was not the case, we could only be certain by knowing the acceptance/rejection rates of positive and negative studies. In fact an NIHR Health Technology Assessment found that publication bias occurs mainly before the presentation of findings at conferences, and before submission of manuscripts to journals [10]. More likely pharmaceutical companies are suppressing studies that are 'bad news' for their profit margin. This is backed up by a study of 546 drug trials registered in 1999 on ClinicalTrials.gov [11]. Trials were sponsored by industry (63%), government sources (14%) or non-profit organisations (23%), and overall 66% had been published. Industry-funded trials had positive outcomes in 85% publications, compared to 50% of government trials, and 72% of non-profit organisations. This significant difference is most likely due to publication bias by the drug companies, although there are other factors that may be involved, for example investigator's failure to write up and submit.

In a study published 15 years ago, 178 abstracts of randomised controlled trials (RCTs) presented at Cystic Fibrosis (CF) conferences were analysed, and in 167 a conclusion could be drawn as to whether the results were positive or negative [12]. There was no difference in the subsequent publication rate between the two categories, although overall it was rather low — 32%. However bias may have already crept in, as 115/167 (69%) of the abstracts presented had positive results. More recently, a study of 142 CF trials registered with ClinicalTrials.gov found that only 44% had been published, after a median of 3.25 years; they found

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http://dx.doi.org/10.1016/j.jcf.2014.01.003

that the source of funding did not influence time to publication, but they did not analyse positive *vs* negative trials [13]. Nevertheless, there are quite a few negative studies published in the CF literature, some of which have made large contributions to our understanding of how best to treat CF. Examples include trials of the leukotriene B_4 antagonist amelubant; recombinant α_1-antitrypsin; inhaled corticosteroids; ataluren (PTC124); ivacaftor for homozygous p.Phe508del mutation; denufosol; nebulised amiloride; miglustat; and high frequency chest wall oscillation (the Vest).

And so to the paper; Elizabeth Tullis et al. present results from the multicentre (35 centres in North America) RCT of three times daily nebulised aztreonam in 100 CF patients with chronic *Burkholderia* infection [1]. Unfortunately the results are disappointing, as despite 24 weeks of continuous nebulised aztreonam, there was no statistical advantage seen compared to placebo for any of their outcomes (lung function, exacerbations requiring antibiotics, or hospitalisations). As usual, the study was powered for change in lung function, and they did at least reach their recruitment target. However there was a 'trend' to less use of intravenous, oral and/or inhaled antibiotics used for any respiratory indication, with the maddening p values of 0.06 and 0.071. One wonders whether that might be a type II error and perhaps aztreonam has some benefits that were missed due to insufficient numbers.

The study was sponsored by Gilead Sciences Inc. and given the discussion above, it is good that the results are in the public domain (they were also presented at the 2011 North American CF Conference). All are to be congratulated as this is the largest study of inhaled antibiotics in CF patients with chronic *Burkholderia* infection. In fact the 2012 Cochrane systematic review found no study of antibiotic use for chest exacerbations in CF patients with chronic *Burkholderia cepacia* complex infection [14]. Furthermore, I am only aware of one other published RCT in CF patients with *Burkholderia cepacia*; nebulised taurolidine was studied in 20 adults [15]. Given the seriousness of this organism, it is rather surprising that so little is published. It is standard to see *Burkholderia* infection as an exclusion criterion for entry into practically every therapeutic trial in CF. Presumably this started out as a logistical issue of patient segregation in research facilities, or perhaps patient numbers were too small in the past, but it almost seems as if there is a prejudice against these patients being in trials. An orphan complication of an orphan disease! This study should help pave the way for further studies to improve the respiratory health of patients with *Burkholderia* infection.

Conflict of interest statement

I have none to declare.

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7 January 2014
Available online xxxx

Please cite this article as: Balfour-Lynn IM, XPATH ERROR: substring() function - wrong number of parameters; at least 2 expected...., J Cyst Fibros (2014), http://dx.doi.org/10.1016/j.jcf.2014.01.003