These letters are selected from rapid responses posted on bmj.com. Selection is usually made 12 days after print publication of the article to which they respond.

LETTERS

SSRIs AND CONGENITAL DEFECTS

Spontaneous publishing and academic miscarriages (SPAM)

In 1991, in the week that the Food and Drug Administration held regulatory hearings on fluoxetine and suicide, the *BMJ* published an article by Lilly employees exonerating fluoxetine, although the article showed a clear increase in risk with treatment and included under the heading of placebo a suicide that had not happened in the randomised phase of the trials.[1 2] This likely played a part in the way academics worldwide viewed the issues. Since then, in my experience, in the run up to major legal trials or regulatory hearings linked to selective serotonin reuptake inhibitors (SSRIs), one or other major journal has run an article exonerating the drug(s).

In the *BMJ* of 26 September Pedersen and colleagues' article on birth defects and SSRIs points to a risk with treatment.[3] It is accompanied by an editorial minimising these risks by Chambers,[4] who has co-authored other pieces advocating the treatment of antenatal depression with antidepressants. Intriguingly, Chambers has a dataset pointing to a significant 5.1-fold increased odds ratio of major birth defects and a 10.8-fold increased odds ratio of cardiac defects with paroxetine, but these data remain unpublished in the peer reviewed literature almost 10 years after they were first generated.[5]

Last month GlaxoSmithKline opened its defence in the first birth defect case linked to paroxetine to go to trial. What odds that its lead counsel brandished the *BMJ* of 26 September in front of jurors? I have no reason to think that any member of the editorial staff of the *BMJ* has been complicit in any wrongdoing, but there does seem to be something here worthy of further investigation. Chambers argues that the risks of non-treatment outweigh the risks of treatment—despite a doubling of the risk of miscarriage. But do the risks of publishing this editorial outweigh the risks of not publishing it? In other words, is there a need for a filter against spontaneous publishing and academic miscarriages (SPAM)?

CHRISTIAN BAITG/GETTY IMAGES

David Healy professor, Department of Psychiatry, Cardiff University **HealyD@cardiff.ac.uk**

Competing interests: DH is a witness for the plaintiff in the legal case mentioned in this letter. A complete list of his competing interests is available at www.bmj.com/cgi/eletters/339/sep23_1/b3525#221140

1 Healy D. Did regulators fail over selective serotonin reuptake inhibitors? *BMJ* 2006;333:92-5.
2 Beasley CM, Dornseif BE, Bosomworth JC, Sayler ME, Rampey AH, Heiligenstein JH. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 1991;303:685-92.
3 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
4 Chambers C. Selective serotonin reuptake inhibitors and congenital malformations. The small risk of harm must be balanced against risk of suboptimal or no treatment. *BMJ* 2009;339:b3525. (23 September.)
5 GSK Medicine: paroxetine. Study No: WEUSRTP2280. Available at: www.gsk-clinicalstudyregister.com/files/pdf/24089.pdf

Cite this as: *BMJ* 2009;339:b4293

We selected Christina Chambers from our reviewer database, which listed her specialist interests as perinatal epidemiology and teratology. She has published on SSRIs in pregnancy, including two articles in the *New England Journal of Medicine* that reported adverse outcomes.—Ed

Author's reply

I did not intend my comments to be interpreted as minimising the risk. Rather, I intended to place the risks in context in terms of both size (which is estimated to be comparatively small compared with other known teratogens such as isotretinoin, which can affect more than 20% of exposed pregnancies) and the concomitant risks of no treatment or undertreatment.

Healy mentions our California data on pregnancy outcomes with prenatal exposure to paroxetine. This is a perfect example of the difficulty in drawing conclusions from studies with inadequate sample sizes. Our data on paroxetine were drawn from an ongoing open cohort study with an increasing but still extremely small sample size. Preliminary results were published in abstract form several years ago,[1] and updated results were provided for and included in the meta-analysis recently published by Wurst et al.[2] These same data were also included in a published paper on the cumulative experience with paroxetine and cardiac defects across several teratology information services.[3] Given that our data on the association with cardiac defects had very wide confidence intervals and lacked significance, we deemed that their contribution was most appropriately evaluated in comprehensive meta-analysis.

My comments in this editorial and elsewhere, consistent with the recent joint guidelines from the American Psychiatric Association and American College of Obstetrics and Gynecology, are intended to support the most appropriate treatment of each mother and fetus, recognising that there may be risks from some treatments, as well as from inappropriate treatment, undertreatment, or no treatment.

Christina Chambers associate professor, Division of Dysmorphology and Teratology, Departments of Pediatrics and Family and Preventive Medicine, School of Medicine, University of California San Diego, 9500 Gilman Drive, MC 0828, La Jolla, CA 92093-0828, USA **chchambers@ucsd.edu**

Competing interests: CC has received grant funding from pharmaceutical companies including Amgen, Abbott, Bristol Myers Squibb, Sanofi-Pasteur, Teva, Sandoz, Kali, Barr, and Apotex, some of which manufacture or distribute selective serotonin reuptake inhibitors (SSRIs).

1 Unfred CL, Chambers CD, Felix R, Kao K, Dick L, Alvarado S, et al. Birth outcomes among pregnant women taking paroxetine (Paxil). Teratology Society 41st annual meeting. June 23-28, 2001, Montreal, Quebec, Canada. Abstracts. *Teratology* 2001;63:211-41.
2 Wurst KE, Poole C, Ephross SA, Olshan AF. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res Part A Clin Mol Teratol* 2009 Sep 8. [Epub ahead of print]
3 Einarson A, Pistelli A, DeSantis M, Malm H, Paulus WD, Panchaud A, et al. Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy. *Am J Psychiatry* 2008;165:749-52.

Cite this as: *BMJ* 2009;339:b4295

Women should give informed consent before starting SSRIs

In Pedersen and colleagues' study of selective serotonin reuptake inhibitors (SSRIs) in pregnancy, the hazards were clearest for citalopram and sertraline.[1] However, a meta-analysis of all epidemiologically robust studies of paroxetine in the first trimester of pregnancy conclusively shows increased prevalence of both cardiac malformations (odds ratio 1.46, 95% confidence interval 1.17 to 1.82) and total malformations (1.24, 1.08 to 1.43).[2]

One of the best signals of teratogenicity is an increased rate of spontaneous abortions and a key reason for induced abortion is congenital malformations.[1] Data on SSRIs in 1998 showed that the rate of abortion (spontaneous and induced) was nearly twice as high in those who had taken SSRIs in the first trimester of pregnancy (1.7, 1.1 to 2.9).[3]

Given the limited evidence for effectiveness and these data on potential hazards for the unborn child, the risk-benefit equation is not favourable for SSRIs in pregnancy. The numbers affected are small, but prescribing is widespread in the reproductive years and the consequences are devastating for families. In contrast to the US recommendations,[4] guidelines from the National Institute for Health and Clinical Excellence (NICE) are consistent with the evidence.[5] NICE recommends stopping SSRIs, paroxetine in particular, in pregnancy (or preferably before) and using alternative treatments or tricyclic antidepressants if pharmacotherapy is unavoidable. As the difficulties in stopping SSRI treatment may lead to unavoidable early exposure of the unborn child, women of reproductive age should give informed consent before starting treatment.

Derelie Mangin associate professor and director, Primary Care Research Unit, Department of Public Health and General Practice, University of Otago, Christchurch, New Zealand
dee.mangin@otago.ac.nz

Competing interests: DM is an expert witness for the plaintiff in cases involving Paxil and birth defects. She is also principal investigator in a New Zealand Health Research Council funded randomised controlled trial of SSRI cessation in primary care. She is a member of and was previously on the management committee of Healthy Skepticism. She has been an invited speaker on aspects of rational prescribing at conferences, some of which were sponsored by pharmaceutical companies.

1 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
2 GSK Medicine: paroxetine. Study No: WEUSRTP2280. Available at: www.gsk-clinicalstudyregister.com/files/pdf/24089.pdf
3 Kulin NA, Pastuszak A, Sage SR, Schick-Boschetto B, Spivey G, Feldkamp M, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998;279:609-10.
4 Chambers C. Selective serotonin reuptake inhibitors and congenital malformations. The small risk of harm must be balanced against risk of suboptimal or no treatment. *BMJ* 2009;339:b3525. (23 September.)
5 National Institute for Health and Clinical Excellence. Antenatal and postnatal mental health. Clinical guidelines CG45. 2007. http://guidance.nice.org.uk/CG45

Cite this as: *BMJ* 2009;339:b4292

SSRIs and heart defects in neonates

In a population study, Pedersen and colleagues found a twofold increased risk of septal heart defects after first trimester exposure to selective serotonin reuptake inhibitors (SSRIs).[1] The prevalence increased with citalopram or sertraline but not paroxetine or fluoxetine, and exposure to more than one type of SSRI posed the greatest risk.

We compared the rate of non-syndromic, non-chromosomal congenital heart malformations in newborn infants exposed to SSRIs and unexposed controls.[2] Every newborn infant with a persistent cardiac murmur (even mild) on the second or third day of life was examined by a paediatric cardiologist and had echocardiography. To our knowledge, this screening approach has not been used in previous studies on SSRI exposure.

Echocardiography identified non-syndromic congenital heart defects in 3.4% of exposed babies and in 1.6% of non-exposed controls (relative risk 2.17, 95% confidence interval 1.07 to 4.39). All heart defects were mild: ventricular septal defect, bicuspid aortic valve, and right superior vena cava to coronary sinus. Although our sample was too small to analyse the effects of specific SSRIs, all four (paroxetine, fluoxetine, citalopram, and sertraline) were associated with heart defects.

Our data and clinical experience suggest that women who require treatment with SSRIs during early pregnancy can be reassured that the risk is small and that possible heart malformations are usually mild and often resolve spontaneously. We advise monitoring during early pregnancy, late-targeted ultrasonography, and fetal echocardiography at 22-23 weeks' gestation. Further larger studies using our approach or other methods are still needed.

Gil Klinger deputy director, Neonatal Intensive Care Unit, Schneider Children's Medical Center of Israel, Petah Tiqwa, 49202, Israel
gilkl@post.tau.ac.il

Paul Merlob Beilinson Teratology Information Service (BELTIS), Rabin Medical Center, Petah Tiqwa, 49100, Israel

Competing interests: None declared.

1 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
2 Merlob P, Birk E, Sirota L, Linder N, Berant M, Stahl B, et al. Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heart murmur. *Birth Defects Res Part A* 2009 Aug 18. [Epub ahead of print]

Cite this as: *BMJ* 2009;339:b4288

Case registers in pregnancy?

Did Pedersen and colleagues[1] find any clinically significant effects of selective seretonin reuptake inhibitors on birth weight, spontaneous abortion, or persistent pulmonary hypertension of the newborn?

Instead of retrospective cohort studies, might case registers for pregnancy and depression similar to prospective epilepsy and pregnancy registers[2] be set up in developed countries with robust monitoring systems by general practitioners and obstetricians? Such registers have achieved prominence with the advent of electronic case records and the technological capacity to derive anonymous databases from them.[3]

Devender Singh Yadav staff grade psychiatrist, Princess of Wales Hospital, Bridgend CF31 1RQ **dsyadav@doctors.org.uk**

Competing interests: None declared.

1 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
2 Morrow J, Russell A, Guthrie E, Parsons L, Robertson I, Waddell R, et al. Malformation risks of anti-epileptic drugs in pregnancy: a prospective study from the UK Epilepsy and Pregnancy Register. *J Neurol Neurosurg Psychiatry* 2006;77:193-8.
3 Perera G, Soremekun M, Breen G, Stewart R. Case register: noble past, challenging present, exciting future. *Br J Psychiatry* 2009;195:191-3.

Cite this as: *BMJ* 2009;339:b4286

See NEWS, p 942

AJ PHOTO/SPL

THIGHS AND HEART DISEASE

Thighs and thresholds

According to the abstract of Heitmann and Frederiksen's paper, "a threshold effect for thigh circumference was evident, with greatly increased risk of premature death below around 60 cm."[1] Table 1 shows that the median thigh circumference was around 55 cm, implying that more than half the population were at greatly increased risk. In contrast to the misleading abstract and press release,[2] the BMJ Group provided a more appropriate interpretation in the *Guardian*: "Having thighs larger than 60 cm made no difference to people's risk. People were most at risk if they had a thigh measurement of less than 46.5 cm (18 inches). This group had roughly double the chances of getting heart and circulation problems or dying during the study. However, only 2.5% of the people fell into this category."[3]

Particularly in men, the reported effects were modest before analyses were adjusted for anthropometric measures such as body mass index and waist circumference. These adjusted estimates are hard to interpret because they refer to the differences in risk that would apply if a person changed his or her thigh circumference while keeping the other anthropometric measures constant.

The accompanying editorial also seemed to ignore these issues in interpretation.[4]

Roger M Harbord medical statistician
roger.harbord@bristol.ac.uk
Jonathan A C Sterne professor of medical statistics and epidemiology, Department of Social Medicine, University of Bristol, Canynge Hall, Bristol BS8 2PS

Competing interests: None declared.

1 Heitmann BL, Frederiksen P. Thigh circumference and risk of heart disease and premature death: prospective cohort study. *BMJ* 2009;339:b3292. (3 September.)
2 BMJ. Press releases Monday 31 August to Friday 4 September 2009. (1) Large thighs protect against heart disease and early death. www.bmj.com/content/vol339/issue7720/press_release.dtl#1
3 BMJ Group. Could big thighs protect against heart disease? *Guardian* 2009 Sep 4. www.guardian.co.uk/lifeandstyle/besttreatments/2009/sep/04/could-big-thighs-protect-against-heart-disease
4 Scott IA. Thigh circumference and risk of heart disease and premature death. *BMJ* 2009;339:b3302. (3 September.)

Cite this as: *BMJ* 2009;339:b4246

Exercise, muscle mass, and insulin sensitivity

Heitmann and Frederiksen found that a small thigh circumference was associated with an increased risk of heart disease or premature death, suggesting that this adverse effect might be related to low muscle mass.[1] Exercise induced increase in muscle mass is associated with improved insulin sensitivity.[2 3]

We measured body composition by dual energy x-ray absorptiometry and insulin sensitivity by oral glucose tolerance testing before and after 12 weeks of aerobic training in 19 overweight and obese girls.[2] We also determined concentrations of adiponectin, C reactive protein, interleukin-6, insulin-like growth factor 1, soluble forms of the cell adhesion molecules ICAM-1 and VCAM-1, lipids, and lipoproteins.

The major finding was a 23.3% improvement in insulin sensitivity after training as shown by the smaller area under the insulin concentration curve (P=0.03). This occurred without changes in body weight, percentage body fat, waist circumference, estimated visceral fat, or serum concentrations of adiponectin, interleukin-6, and C reactive protein. Lower limb fat free mass increased with training by 6.2% (P<0.01), and was inversely correlated with the area under the insulin concentration curve (r=−0.68, P<0.01).

George P Nassis research associate, Department of Sport Medicine and Biology of Physical Activity, Faculty of Physical Education and Sport Science, National and Kapodistrian University of Athens, Athens, Greece **gnassis@phed.uoa.gr**
Labros S Sidossis professor, Laboratory of Nutrition and Clinical Dietetics, Department of Nutrition and Dietetics, Harokopio University, Athens

Competing interests: None declared.

1 Heitmann BL, Frederiksen P. Thigh circumference and risk of heart disease and premature death: prospective cohort study. *BMJ* 2009;339:b3292. (3 September.)
2 Nassis GP, Papantakou K, Skenderi K, Triandafillopoulou M, Kavouras SA, Yannakoulia M, et al. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin and inflammatory markers in overweight and obese girls. *Metabolism* 2005;54:1472-9.
3 Potteiger JA, Jacobsen DJ, Donnelly JE, Hill JO. Glucose and insulin responses following 16 months of exercise training in overweight adults: the Midwest Exercise Trial. *Metabolism* 2003;52:1175-81.

Cite this as: *BMJ* 2009;339:b4249

Great Danes

Shouldn't there be some sort of recognition—perhaps a prize—for the way the Danes keep producing interesting and useful population research? In one issue alone, the *BMJ* published Danish research on the safety of selective serotonin reuptake inhibitors in pregnancy and the association of thigh circumference with risk of heart disease and premature death.[1 2] Recently it published a useful long term study on the contraceptive pill and blood clots.[3] Then there is the Nordic Cochrane Centre and its very good studies on, for example, the harms of breast screening.[4]

How have the Danes done all this? Identity cards, a reliable population database, and a national registry of all prescriptions notwithstanding, it is commendable how they have utilised their systems for research. The rest of the world should express some appreciation.

I wonder whether Danish systems cost as much as the NHS National Programme for Information Technology?[5]

Ted Willis general practitioner, Brigg, North Lincolnshire
ted@docwillis.co.uk

Competing interests: None declared.

1 Pedersen LH, Henriksen TB, Vestergaard M, Olsen J, Bech BH. Selective serotonin reuptake inhibitors in pregnancy and congenital malformations: population based cohort study. *BMJ* 2009;339:b3569. (23 September.)
2 Heitmann BL, Frederiksen P. Thigh circumference and risk of heart disease and premature death: prospective cohort study. *BMJ* 2009;339:b3292. (3 September.)
3 Lidegaard O, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009;339:b2890. (13 August.)
4 Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. *BMJ* 2009;339:b2587. (9 July.)
5 Cross M. Can the NHS get connected? *BMJ* 2009;339:b3647. (24 September.)

Cite this as: *BMJ* 2009;339:b4251

EQUITY AND NHS REFORMS

What about independent sector treatment centres?

Cooper and colleagues have ignored the government's £5 billion independent sector treatment centre (ISTC) programme in explaining the narrowing of the gap in waiting times across social classes.[1-3] Patients attending such centres are routine and straightforward elective cases—that is, without complications and co-morbidities—and will have shorter waiting times. Compared with the rest of the NHS, ISTCs also treat fewer patients in lower socioeconomic groups.[4]

Lack of data and incomplete and poor quality data returns are hallmarks of the ISTC programme, in which cataract surgery, knee and hip replacement, and other treatments are delivered to NHS patients by for-profit companies in mainly private facilities. Although all ISTCs are required to submit hospital episode statistics on all NHS patients treated, the Healthcare Commission found that during 2005-6 fewer than half of them returned any data.[4] Of the data returned, 43.4% were missing primary procedure codes and 7.6% had invalid primary procedure codes.[5] For 2006-7, 18.8% of episodes were missing primary procedure codes and 1.3% were invalid.[5]

Lack of data returns and incomplete data will seem to reduce the social class gradient in waiting times since ISTCs treat more patients from higher social classes with shorter waiting times. As a result, Cooper and colleagues cannot rule out data artefact as a critical explanation for the apparent improvements in equity.

Allyson M Pollock professor and director
allyson.pollock@ed.ac.uk
Sylvia Godden senior research fellow
Graham Kirkwood research fellow, Centre for International Public Health Policy, University of Edinburgh, Edinburgh EH8 9AG

Competing interests: None declared.

1 Cooper ZN, McGuire A, Jones S, Le Grand J. Equity, waiting times, and NHS reforms: retrospective study. *BMJ* 2009;339:b3264. (3 September.)
2 Pollock AM, Godden S. Independent sector treatment centres: evidence so far. *BMJ* 2008;336:421-4.
3 Pollock AM, Kirkwood G. Is the private sector better value for money than the NHS? A Scottish case study. *BMJ* 2009;338:b1421.
4 Healthcare Commission. Independent sector treatment centres. A review of the quality of care. 2007. www.cqc.org.uk/_db/_documents/ISTC_Final_Tagged_200903243502.pdf
5 Healthcare Commission. Independent sector treatment centres: the evidence so far. 2008. www.cqc.org.uk/_db/_documents/Independent_sector_treatment_centres_The_evidense_so_far.pdf

Cite this as: *BMJ* 2009;339:b4255

PROSTATE SPECIFIC ANTIGEN

French exceptionalism

Holmström and colleagues confirm that no single cut-off value for prostate specific antigen concentration attained likelihood ratios formally required for a screening test.[1] However, the number of men who would need to be offered screening to prevent one death from prostate cancer during a 10 year period is not 1068 but 1410.[2]

JOHN CURTIS/REX

Everywhere, practice guidelines are up to date and clearly cite the unproved benefit of screening for prostate specific antigen, as well as the adverse effects (high risk of overdiagnosis and overtreatment).[3] Everywhere, that is, but in France. For the fifth consecutive year, French urologists are actively promoting prostate cancer screening,[4] despite the arguments.[5]

Alain Braillon doctor, Public Health, University Hospitals, 80000 Amiens, France **braillon.alain@chu-amiens.fr**

Competing interests: None declared.

1 Holmström B, Johansson M, Bergh A, Stenman UH, Hallmans G, Stattin P. Prostate specific antigen for early detection of prostate cancer: longitudinal study. *BMJ* 2009;339:b3537. (24 September.)
2 Barry MJ. Screening for prostate cancer—the controversy that refuses to die. *N Engl J Med* 2009;360:1351-4.
3 NHS Cancer Screening Programmes. Prostate cancer risk management. www.cancerscreening.nhs.uk/prostate/index.html
4 Association Française d'Urologie. 5ème Journée de la Prostate. www.urofrance.org/espace-general/actions-information/journee-prostate/journee-prostate-2009.html
5 Braillon A, Dubois G, Zielinski O. Screening for prostate cancer: a public campaign, evidence-based-medicine and conflicting interests. *Eur J Public Health* 2009;19:222.

Cite this as: *BMJ* 2009;339:b4285

CAPSULE ENDOSCOPY

Technique has limitations

Capsule endoscopy has become an essential tool in investigating small bowel disease.[1] However, a recent paper describes its limitations compared with optical colonoscopy in detecting both polyps and cancers.[2]

Whereas capsule colonoscopy seems less invasive, it still requires bowel preparation, which many patients find as unpleasant as undergoing optical colonoscopy. Furthermore, in their study of 328 cases Van Gossum et al found that its sensitivity and specificity in detecting colonic polyps greater than 6 mm was only 64% and 84% respectively compared with optical colonoscopy.[2] Similarly, of 19 cancers diagnosed at optical colonoscopy, only 14 were detected by capsule endoscopy. Currently optical colonoscopy can be performed in a suboptimally cleansed colon, with the possibility of clearing colonic debris during the procedure, and insufflating air into collapsed intestines. This is not the case for capsule colonoscopy.

These data show that capsule endoscopy is not a screening tool for colonic neoplasia but should be used only in selected patients with a particular dislike of optical colonoscopy.

Andy Li consultant gastroenterologist, Western Sussex Hospitals NHS Trust **andy.li@wsht.nhs.uk**

Competing interests: AL has received hospitality and education sponsored by Diagmed UK and Given Imaging.

1 Moglia A, Pietrabissa A, Cuschieri A. Capsule endoscopy. *BMJ* 2009;339:b3420. (11 September.)
2 Van Gossum A, Munoz-Navas M, Fernandez-Urien I, Carretero C, Gay G, Delvaux M, et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. *N Engl J Med* 2009;361:264-70.

Cite this as: *BMJ* 2009;339:b4282

RESPONSE: **Tom MacDonald**

Tom MacDonald replies to Marisa de Andrade

Thank you for allowing me to respond to Ms Andrade's article about the Standard Care versus Celecoxib Outcome Trial (SCOT).[1]

SCOT was designed by me with Professor C J Hawkey (Nottingham University) and Professor Ian Ford (Glasgow University). The protocol is the property of Dundee University (the study sponsor) and was formally approved by the European Medicines Evaluation Agency (EMEA), as well as other regulatory bodies. The aim of the study is to assess the long term drug safety of non-steroidal anti-inflammatory drugs (NSAIDs) and is funded by Pfizer USA. In general the pharmaceutical industry does not see such safety studies as attractive commercially, which is why SCOT is led by an independent investigator (me) and managed by an academic steering committee.

The meeting served several functions: education about the toxicity of NSAIDs (the meeting was accredited by EPASS (Educational Providers Accreditation Scheme (Scotland)); training in trial methods; a description of the SCOT study; detailed training on the web portal and IT issues; and good clinical practice (GCP) training. The trial requires at least one but preferably more general practitioners in each practice to be trained in the protocol, and this and GCP training are considered mandatory by regulatory authorities.

The financial support of Pfizer for SCOT was clearly communicated in meeting slides, press releases, and published articles. Unfortunately the www.ClinicalTrials.gov website cited by Ms Andrade has no separate field to include the study funder, and so we had no opportunity to enter this information. There is obviously confusion about the term sponsor, which has a precise meaning in EU legislation and does not mean funder. In this case the University of Dundee is the trial sponsor.

This trial budget for such a large study is substantial, but it is a sobering fact that this is about a fifth of the cost of standard industry-run studies. In this case, funding is required for the Robertson Centre for Biostatistics in Glasgow University for the data centre and for the staffing costs at each of the clinical centres of the Universities of Aberdeen, Dundee, Edinburgh, Glasgow, and Southern Denmark, and the remainder of the funding goes on direct trial costs with a relatively small amount spent on practice training and recruitment.

We agree that practices interested in research are easier to recruit and that they will willingly attend evening meetings in academic venues "for the science." However, we have currently recruited over 290 practices into the SCOT study (target: 500 or more). These are all extremely busy practices, many of them servicing deprived areas. Most have not previously done much research. Such practices need both training and a thorough briefing to reassure them that the research will not overwhelm them with work. In addition, an evening meeting would not provide enough time to cover all of the required issues.

The choice of venue was made by me as principal investigator, and me alone. It was taken after an option appraisal of all the other venues. Invitations to practices were Scotland-wide so a central venue was vital. Other hotels were either more expensive or lacked sufficient accommodation or an adequate meeting room or were undergoing extensive renovations.

There are many positive aspects of SCOT that could and, in my view, should be celebrated. I wonder if the *BMJ* editor might kindly commission me to write 2400 words on the good news about SCOT?

Tom MacDonald professor of clinical pharmacology, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY **tom@memo.dundee.ac.uk**

Competing interests: A full list of competing interests is given in the longer version of this response at www.bmj.com/cgi/eletters/339/sep02_1/b3443#222055

1 de Andrade M. In clear sight. *BMJ* 2009;339:b3443. (2 September.)

Cite this as: *BMJ* 2009;339:b4281

The Response column is designed to give those who have been written about in the *BMJ* a chance to reply at slightly longer length (650 words maximum) than is possible on our letters pages. Submissions should be emailed directly to the editor (editor@bmj.com) and clearly labelled "Response column." Submissions that are printed may need to be edited. The editor maintains the right to decide whether or not to grant space in our Response column.