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LETTERS

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DUTCH PERINATAL MORTALITY

Too early to question effectiveness of Dutch system

The study by Evers et al is the first to show a higher mortality among births that started in primary care compared with secondary care.[1] We have concerns about the methods used.

Firstly, although the title suggests that it is a prospective cohort study, the entire population at risk was defined retrospectively and based on postal codes of the catchment area of one university hospital. All intrapartum and neonatal deaths were included from hospitals and midwifery practices in this area, but potentially not all births. Midwives in practices at the periphery of the catchment area will also care for many women in neighbouring regions. These births have not been included in the study unless the baby died. This will artificially inflate mortality in midwifery practices.

Secondly, the study was conducted in only one region in the Netherlands. Intrapartum mortality and neonatal mortality were twice as high as in recent national studies among women in primary care at the onset of labour (1.39 *v* 0.65 and 0.52 per 1000).[2 3] Although classification bias and under-reporting may have played a part in these retrospective studies, half of all deaths are unlikely to have been missed. In another prospective study of perinatal mortality only 3.5% additional cases were found compared with national registration data.[4] This discrepancy suggests that the study sample may be rather different from the national population.

Previous audit studies did not find that features of the Dutch maternity care system were related to preventable perinatal deaths.[4 5] Given the limitations of the study, the suggestion that the obstetric care system in the Netherlands may contribute to the high perinatal mortality cannot be made on the basis of these data alone.

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Competing interests: None declared.

1 Evers ACC, Brouwers HAA, Hukkelhoven CWPM, Nikkels PGJ, Boon J, van Egmond-Linden A, et al. Perinatal mortality and severe morbidity in low and high risk term pregnancies in the Netherlands: prospective cohort study. *BMJ* 2010;341:c5639. (2 November.)
2 Amelink-Verburg MP, Verloove-Vanhorick SP, Hakkenberg RM, Veldhuijzen IM, Bennebroek GJ, Buitendijk SE. Evaluation of 280,000 cases in Dutch midwifery practices: a descriptive study. *BJOG* 2008;115:570-8.
3 De Jonge A, Van der Goes BY, Ravelli AC, Amelink-Verburg MP, Mol BW, Nijhuis JG, et al. Perinatal mortality and morbidity in a nationwide cohort of 529,688 low-risk planned home and hospital births. *BJOG* 2009;116:1177-84.
4 Wolleswinkel-van den Bosch JH, Vredevoogd CB, Borkent-Polet M, van EJ, Fetter WP, Lagro-Janssen TL, et al. Substandard factors in perinatal care in The Netherlands: a regional audit of perinatal deaths. *Acta Obstet Gynecol Scand* 2002;81:17-24.
5 Bais JM, Eskes M, Bonsel GJ. [The determinants of the high Dutch perinatal mortality in a complete regional cohort, 1990-1994]. *Ned Tijdschr Geneeskd* 2004;148:1873-8.

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Results don't seem generalisable

Evers and colleagues do not mention any data on the number of women who deliver at home, in hospital with a community midwife, and in hospital after referral from primary to secondary care.[1] They give several explanations without exploring them: "The community midwife is not present during the first hours after labour started at home." However, the Dutch Perinatal Registry showed that most referrals to secondary care occurred after the first hours of labour.[2] Evers and colleagues also say: "There might be a time-delay because of transport to the hospital in case of emergency." But how many women starting labour with the community midwife were already in hospital before they were referred to secondary care?

The best way to answer the question of where to confine is to randomise low risk women to primary or secondary care delivery. Obviously, no low risk pregnant woman will accept randomisation for the benefit of research. An alternative is an "open" prospective study in which important known confounders of perinatal death are included. But Evers and colleagues did not include any confounder in their analysis.. Also, the number of low risk women who started labour in primary care was 5% higher than mentioned in the Dutch Perinatal Registry,[2] which also shows that 8% of all high risk pregnant women who deliver in secondary care are in fact at low risk. So, there were more low risk women starting labour in primary care than expected, while in the high risk group a substantial number were in fact low risk.

We wonder whether this could have interfered with the perinatal death figures. Or is the cohort not representative for the country, thus not allowing the authors to generalise their findings?

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1 Evers ACC, Brouwers HAA, Hukkelhoven CWPM, Nikkels PGJ, Boon J, van Egmond-Linden A, et al. Perinatal mortality and severe morbidity in low and high risk term pregnancies in the Netherlands: prospective cohort study. *BMJ* 2010;341:c5639. (2 November.)
2 Netherlands Perinatal Registry. Perinatal care in the Netherlands 2007.

Cite this as: *BMJ* 2010;341:c7022

Authors' reply

De Jonge and colleagues and Pop and Wijnen commented on the nomenclature of our study.[1 2] We performed a cohort study, including cases in a prospective manner. Thus important problems associated with retrospective data collection—such as dependence of the investigator on the availability and accuracy of medical case records and classification bias of the cases—are prevented. The population at risk was estimated retrospectively using aggregated, prospectively collected data from the national perinatal register. We emphasised these limitations in our paper.

De Jonge and colleagues are concerned that mortality in midwifery practices may be artificially inflated. To show that our findings were not caused by under-reporting of normal births we did artificially increase the denominator by 10% in the paper without any difference in model outcome. If we increase the denominator by another 5%, accounting for the possibility that we have missed births from the periphery of our catchment area, the findings still remain robust.

De Jonge and colleagues and Pop and Wijnen note the discrepancy between our results and those of previous studies.[3 4] Notwithstanding the differences in study design, our perinatal mortality among term infants without congenital anomalies, 2.6 per 1000, is similar to that in large nationwide studies.[5 6] Classification problems in databases might explain the differences.

To our knowledge, ours is the only study in the Netherlands showing a higher risk of delivery related perinatal mortality among women with the intention to deliver in primary care compared with women who start delivery in secondary care. Given the limitations of the study, we agree that our study design cannot show a causal association between the results and (specific parts of) the obstetric care system. We emphasise that we only philosophised about possible explanations and solutions in the discussion and hope that our paper will stimulate further discussion that may lead to improvement in outcome for newborn infants.

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Competing interests: None declared.

1 De Jonge A, Mol BM, van der Goes BY, Nijhuoris JG, van der Post JA, et al. Too early to question effectiveness of Dutch system. *BMJ* 2010;341:c7020.
2 Pop VJ, Wijnen H. Results don't seem generalisable. *BMJ* 2010;341:c7022.
3 Amelink-Verburg MP, Verloove-Vanhorick SP, Hakkenberg RM, Veldhuijzen IM, Bennebroek GJ, Buitendijk SE. Evaluation of 280,000 cases in Dutch midwifery practices: a descriptive study. *BJOG* 2008;115:570-8.
4 De Jonge A, Van der Goes BY, Ravelli AC, Amelink-Verburg MP, Mol BW, Nijhuis JG, et al. Perinatal mortality and morbidity in a nationwide cohort of 529,688 low-risk planned home and hospital births. *BJOG* 2009;116:1177-84.
5 Ravelli ACJ, Eskes M, Tromp M, Van Huis AM, Steegers EAP, Tamminga P, et al. Perinatal mortality in the Netherlands 2000-2006: risk factors and risk selection. *Ned Tijdschr Geneesk* 2008;152:2728-33.
6 Zeitlin J, Mohangoo A, Cuttini M, EUROPERISTAT Report Writing Committee, Alexander S, Barros H, et al. The European perinatal health report: comparing the health and care of pregnant women and newborn babies in Europe. *J Epidemiol Community Health* 2009;63:681-2.

Cite this as: *BMJ* 2010;341:c7023

Study did a good job

The *BMJ* and several Dutch national newspapers published many criticisms of the methods of the Utrecht study on perinatal mortality in the Netherlands.[1] These include: the numbers in Utrecht differ from those in another study, and therefore can't be right; there was no correction for confounders; the number of midwife deliveries with live births was underestimated; the study wasn't really prospective; and there was no protocol in advance. When the consequences of these criticisms are weighed, they do not detract from the findings.

The results of the low risk group differ from previous results[2] because different groups and a different comparison were studied. The missing correction for confounders would only have made the results stronger because low risk deliveries are kept under the supervision of midwives, while high risk deliveries are referred to obstetricians during pregnancy or during delivery. Looking at the underestimation of live births delivered by midwives, only if in reality the number of live births was two to three times larger would the results have been the other way around.

According to the STROBE guidelines,[3] there are three definitions of prospective, of which one was used. Also, a protocol is not a sine qua non. In this type of research, it does not matter that an analysis was not prespecified: data are data. If an unexpected result is found, such as a severe adverse effect in a study that was designed for other purposes, it still needs to be considered in the light of previous knowledge, and needs to be published.

"The best (re)analysis of a study is to repeat it."[4] This is possible, and preliminary results are known to be available from other regions in the Netherlands.

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Competing interests: None declared.
An extended version of these views was published as a rapid response.

1 Evers ACC, Brouwers HAA, Hukkelhoven CWPM, Nikkels PGJ, Boon J, van Egmond-Linden A, et al. Perinatal mortality and severe morbidity in low and high risk term pregnancies in the Netherlands: prospective cohort study. *BMJ* 2010;341:c5639. (2 November.)
2 De Jonge A, Van der Goes BY, Ravelli AC, Amelink-Verburg MP, Mol BW, Nijhuis JG, et al. Perinatal mortality and morbidity in a nationwide cohort of 529,688 low-risk planned home and hospital births. *BJOG* 2009;116:1177-84.
3 Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med* 2007;4(10):e297.
4 Cornfield J. The University Group Diabetes Program. A further statistical analysis of the mortality findings. *JAMA* 1971;217:1676-87.

Cite this as: *BMJ* 2010;341:c7042

STOCKHOLM NETWORK

CEO replies

Harkins and Jones question the Stockholm Network's ability to produce independent research since we receive industry funding.[1]

The funding sources of policymaking organisations such as think tanks ought to be transparent whenever possible. We receive memberships and research grants from companies, foundations, and individuals. we list all sponsors on our website and in our annual reports and most of the material cited by Harkins and Jones as evidence for our industry bias is provided by our own reports. This allows people to reach their own conclusions, both in light of our funding and, most importantly, from the substance of our research. However, Harkins and Jones's criticism is aimed purely at our (openly declared) funding, not at what we say—this is, after all, the easier target.

Allegations of lobbying are easy to make and essentially impossible to refute when unsubstantiated. This is why journals such as the *BMJ* now insist on a declaration of competing interests. Harkins and Jones's Powerbase project was set up by Spinwatch to be critical of think tanks, particularly those with a pro-market stance, and is funded by foundations, some of which have an explicit anti-globalisation agenda. It is therefore not surprising that they may have an ideological opposition to our work. Yet they provide no information in their article about sources of their own funding.

Fair criticism of a think tank's work in a scientific journal should be based on the merits of the research rather than its funding sources alone or on a political agenda which opposes the existence of such think tanks in the first place.

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Competing interests: HED is responding to criticism of the organisation she runs.

1 Harkins S, Jones M. The Stockholm Network. *BMJ* 2010;341:c6413. (11 November.)

Cite this as: *BMJ* 2010;341:c7013

Authors' reply

Helen Disney, chief executive of the Stockholm Network, a private company that coordinates the work of over 100 freemarket think tanks, argues that funding sources for research carried out by policymaking organisations such as think tanks ought to be transparent whenever possible.[1] She claims that "we list all sponsors on our website and in our annual reports" and that funding is openly declared. In fact, Disney does not publicly disclose how much money she gets from Pfizer, GSK, and Merck or the other corporate interests that bankroll her operation.

This raises questions over how closely research produced by the Stockholm Network correlates to its sponsors' commercial interests. One sponsor, Pfizer, spent $21.9m (£14m; €17m) on lobbying in the US last year.[2] The links between Pfizer and the Stockholm Network raise legitimate concerns about lobbying activity, including the involvement of a Pfizer executive in setting it up.[3] We argue that until the network makes public the amounts from each sponsor it will remain unable to refute lobbying allegations or claim that it has openly declared funding.

Powerbase is a project of the non-profit Spinwatch, set up to promote transparency and shine a light on people and groups shaping the public agenda. It is not anti-think tank or ideologically opposed as Disney contends but believes that it is valid to investigate potential conflicts of interest and ask in whose interests think tanks operate. That is why Spinwatch is pushing for think tanks to be included on the statutory register of lobbyists the government is committed to introducing. Spinwatch publishes its own funders' amounts on its website.[4] For transparency's sake, Stockholm Network should do the same.

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Competing interests: None declared.

1 Disney H. CEO replies. *BMJ* 2010;341:c7013.
2 Centre for Responsive Politics, Lobbying: Pfizer Inc. Opensecrets.org. www.opensecrets.org/lobby/firmsum.php?lname=Pfizer+Inc&year=2009.
3 Galen Institute. Catherine Windels. Officers and trustees. www.galen.org/content/officersandtrustees.
4 Spinwatch. Who funds Spinwatch? www.spinwatch.org.uk/about-spinwatch-mainmenu-13/3705-who-funds-spinwatch.

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FOOD AND DRUG ADMINISTRATION

FDA is gold standard of review

Brownlee and Lenzer had clearly made up their minds about the Food and Drug Administration (FDA) and medical device community before writing their article.[1] It is unfortunate that they didn't acknowledge the cutting edge advances and improvements to patient care medical devices provide every day.

Today, with such medical advances, the average American can expect to live to 78, a 65% increase over the past 100 years. The medical device industry is perhaps one of the greatest unsung contributors to increased life expectancy. Research has shown that since 1980 death rates have declined 16% and Americans spend 56% fewer days in hospital, partly because of medical devices.

Brownlee and Lenzer seem quick to focus on select instances of unfortunate results, while failing to acknowledge the overwhelming success rate and positive experiences of millions of Americans each year. A recent study of FDA approved medical devices from the past five years showed that less than 1% were recalled.[2] Most recalls were attributed to manufacturing and design problems in a postmarketing setting.

Perhaps worse, they rely on "expert" commentary by two people with a long history of unfair and unfounded criticism towards regulators and medical device manufacturers.

Both the FDA and medical device industry share common goals to ensure patient safety and promote innovation so that patients can lead healthier more productive lives. Perhaps the next time these authors decide to look at one of America's most innovative and patient driven industries they will acknowledge this part of the story.[2]

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Competing interests: None declared.

1 Lenzer J, Brownlee S. Why the FDA can't protect the public. *BMJ* 2010;341:c4753. (2 November.)
2 Hall RF. Using recall data to assess the 510(k) process. 2010. www.iom.edu/~/media/Files/Activity%20Files/PublicHealth/510kProcess/2010-JUL-28/06%20Hall.pdf.

Cite this as: *BMJ* 2010;341:c7004

Surveillance and medical devices

Lenzer and Brownlee highlight the potential value for postmarketing surveillance,[1] but this is true not only for "complex" or new devices.

The UK government's decision in 2001 to replace reusable tonsillectomy instruments with single use devices, because of the risk from variant Creutzfeldt-Jakob disease, is a lesson in point. These were not complex devices, but widespread adverse events followed, and they were subsequently withdrawn in England. In Wales, we did not return to reusable instruments, but tonsillectomy temporarily ceased before the procurement and introduction of specified single use instruments, which were then surveyed in use.[2]

The product evaluation stage showed that some single use instruments were unfit for purpose, despite being CE marked. Similar problems have been seen with other reusable surgical instruments,[3] suggesting that the regulation of medical devices needs reassessment and modernisation.

The surveillance system was key to identifying and correcting problems and has enabled us to show that products procured in this way are safe.[4] Importantly, adverse clinical events and individual device behaviour were included. This provided a better understanding of complications or instrument failures and the route to an improved or safer device.

Establishing such comprehensive surveillance is not easy. The Welsh Assembly government provided essential strategic direction and initial funding, but the key to our success was the coordinated inclusion of all the main stakeholders. Recognition of and involvement with surveillance systems by regulatory bodies would provide additional authority and confidence in this type of work for the public, clinicians, the medical device industry, and healthcare policy makers.

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Competing interests: None declared.

1 Lenzer J, Brownlee S. Why the FDA can't protect the public. *BMJ* 2010;341:c4753. (2 November.)
2 Tomkinson A, Phillips P, Scott JB, Harrison W, De Martin S, Backhouse SS, et al. A laboratory and clinical evaluation of single-use instruments for tonsil and adenoid surgery. *Clin Otolaryngol* 2005;30:135-42.

3 Brophy T, Srodon PD, Briggs C, Barry P, Steatham J, Birch MJ. Quality of surgical instruments. *Ann R Coll Surg Engl* 2006;88:390-3.
4 Tomkinson A, Harrison W, Owens D, Harris S, McClure V, Temple M. Risk factors for postoperative hemorrhage following tonsillectomy. *Laryngoscope* 2010; online 16 November; doi:10.1002/lary.21242.

Cite this as: *BMJ* 2010;341:c6999

ORPHAN DRUGS

BioMarin Europe replies

Among the inaccuracies in the open letter of Nicholl and colleagues,[1] is the statement that the chemical 3,4-diaminopyridine base (3,4-DAP) has an excellent safety record. This cannot be substantiated by evidence since 3,4-DAP has not undergone systematic safety and toxicology testing nor does it have appropriate safety monitoring and pharmacovigilance systems in place to capture, analyse, and report such data. 3,4-DAP is not a generic drug but a chemical prescribed as a "special."

Studies with 3,4-DAP have shown dose dependent serious adverse drug reactions such as epileptic seizure and cardiac arrhythmia, and even at low doses 18% of patients reported adverse drug reactions.[2 3]

Analysis of 3,4-DAP from nine manufacturers showed a variability in content of active ingredient of 22.2-125.2%.[4] None of the samples met the standard for good manufacturing practice which amifampridine is required to adhere to. For a drug with an upper therapeutic range with regard to serious, life threatening side effects, this exposes patients to unnecessary risk.

The marketing authorisation of amifampridine was based on preclinical toxicology and safety studies, clinical studies to ensure bioequivalence, and safety data from a three year open label early access programme in more than 80 patients.[5] Additional clinical studies have since been finalised or are under way.

BioMarin submitted data for the Pharmaceutical Price Regulation Scheme. The Department of Health confirmed that it is satisfied with the data and had no further questions. BioMarin has since lowered the price of amifampridine in the UK by 10%, in line with the approved price in France. The maximum cost to the NHS when prescribed to all adult patients with Lambert-Eaton myasthenic syndrome at maximum dose according to the summary of product characteristics is less than £6m (€7m; $9m) a year.

In amifampridine adult patients with Lambert-Eaton myasthenic syndrome in Europe have a pharmaceutical grade drug with the required safeguards in place as they deserve.

The full version of this response is available at www.bmj.com/content/341/bmj.c6587/reply#bmj_el_245387.

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Competing interests: AQ and JL are employees of BioMarin Europe.

1 Nicholl DJ, Hilton-Jones D, Palace J, Richmond S, Finlayson S, Winer J, et al. Open letter to prime minister David Cameron and health secretary Andrew Lansley. *BMJ* 2010;341:c6466. (16 November.)
2 McEvoy KM, Windebank AJ, Daube JR, Low PA. 3,4-diaminopyridine in the treatment of Lambert-Eaton myasthenic syndrome. *N Engl J Med* 1989;321:1567-71.
3 Flet L, Polard E, Guillard O, Leray E, Allain H, Javaudin L, et al. 3,4-Diaminopyridine safety in clinical practice: an observational, retrospective cohort study. *J Neurol* 2010;257:937-46.
4 Green DM, Jones AC, Brain K., Active content variability of compounded 3,4-diaminopyridine in solid oral dosage forms. (Abstract.) *Acta Myologica* 2010:29(TW24):217-8. (Poster presented at the 12th international congress on neuromuscular diseases, Naples, July 2010.)
5 European Medicines Agency. Assessment report for Zenas, International Nonproprietary Name: amifampridine. Procedure No: EMEA/H/C/001032. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001032/WC500069918.pdf.

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Viridian Pharma replies

In their open letter Nicholl and colleagues say that caffeine treatment for apnoea of prematurity has been subject to "massive" price rises in recent years as a result of being a treatment for a designated orphan disease.[1] This is not the case in the UK. Caffeine injection for treatment of apnoea of prematurity is manufactured and sold in the UK by Martindale Pharma. The marketing authorisation is held by Viridian Pharma, but it was not granted under an orphan drug status.

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Competing interests: Viridian Pharma is the UK marketing authorisation holder for caffeine 5 mg/ml solution for injection, licensed for oral or intravenous treatment of apnoea of prematurity.

1 Nicholl DJ, Hilton-Jones D, Palace J, Richmond S, Finlayson S, Winer J, et al. Open letter to prime minister David Cameron and health secretary Andrew Lansley. *BMJ* 2010;341:c6466. (16 November.)

Cite this as: *BMJ* 2010;341:c7010

Regulation is flawed

Something is fundamentally wrong with a drug regulatory system that makes it increasingly difficult to do independent pragmatic trials of widely used but unproven drugs yet licenses a ridiculously expensive drug with no randomised evidence that it improves clinical outcomes over the cheap unlicensed preparation.[1 2]

Quality control is important, but the company's argument that the 50-fold increase in price over the unlicensed preparation is partly justified by better pharmacokinetics and better safety monitoring is highly questionable. At the least they should have had to do a randomised trial against the existing preparation to show that their product improves patients' symptom control and safety. Such a trial is still possible (a crossover trial, which would reduce the necessary sample size, might do), ideally with an independent cost effectiveness analysis to show value for money. Patient recruitment should not be a problem if patients are told that without such a trial treatment costs will escalate to a point where some funders will refuse to pay.

Everyone I have spoken to in the Scottish neurology community supports Nicholl and colleagues' call for an urgent review of the decision on 3,4-diaminopyridine and the generic problem of licensing orphan drugs that it highlights. Given the spiralling cost of drugs for the NHS, should some expensive drugs—orphan or otherwise—be given licences only to be used in the context of national randomised trials to prove their worth?

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Competing interests: CEC is a practising neurologist who has treated patients with unlicensed 3,4 diaminopyridine.

1 Nicholl DJ, Hilton-Jones D, Palace J, Richmond S, Finlayson S, Winer J, et al. Open letter to prime minister David Cameron and health secretary Andrew Lansley. *BMJ* 2010;341:c6466. (25 November.)
2 Hawkes N, Cohen D. What makes an orphan drug? *BMJ* 2010;341:c6459. (25 November.)

Cite this as: *BMJ* 2010;341:c7016

Dutch situation is similar

I fully agree with the authors' analysis.[1] The situation in the Netherlands is the same. As a further example to those given by Ferner and Hughes, zinc sulfate has been used in the Netherlands for years to treat Wilson's disease (copper excretion defect). Zinc sulfate liquid was prepared by pharmacists for about €100 (£85; $133) a year (including preparation fee and ingredients). But a drug company has registered zinc acetate capsules as an orphan drug on the basis of studies that often looked at zinc salts other than zinc acetate. The registration of this drug that costs €1750 a year means that pharmacists will no longer be allowed to make up the cost effective alternative.

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Competing interests: MB is a community pharmacist, member of a committee on appreciation of the therapeutic value of pharmaceuticals in the Netherlands (CFH).

1 Ferner RE, Hughes DA. The problem of orphan drugs. *BMJ* 2010;341:c6456. (18 November.)

Cite this as: *BMJ* 2010;341:c7018