EDITORIALS

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News: Cancer charity demands extension of drug fund despite criticisms it is unfair (*BMJ* 2014;349:g6507)
Feature: Peter Clark: public attitudes support a more favourable assessment for cancer treatments (*BMJ* 2014;349:g5545)
Feature: Which way now for the Cancer Drugs Fund? (*BMJ* 2014;349:g5524)

Reforming the Cancer Drugs Fund

Focus on drugs that might be shown to be cost effective

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The Cancer Drugs Fund was originally conceived as a temporary measure, until value based pricing for drugs was introduced, to give NHS cancer patients access to drugs not approved by NICE. Spending on these drugs rose from less than the £50m (€63m; $79m) budgeted for the first year in 2010-11 to well over £200m in 2013-14, and the budget for the scheme—now extended for a further two years—will reach £280m by 2016.[1] The recent changes to the fund recognise the impossibility of providing all the new cancer drugs that offer possible benefit to patients. More radical changes are needed to the working of the fund, given the failure to introduce value based pricing, so that it deals with the underlying problem of inadequate information on the effectiveness and cost effectiveness of new cancer drugs when used in the NHS.

A recent *The BMJ* briefing identified major problems with the fund.[2] The opportunity costs in terms of the treatments that cannot, as a result, be afforded elsewhere in the NHS are substantial, with consequent decrements to other patients' health. Its operation undermines the role of the National Institute for Health and Care Excellence (NICE). A rejection from NICE on the grounds that a drug is not cost effective (at the price proposed by the company) means little if the NHS funds it anyway through the Cancer Drugs Fund. The fund's existence means that companies have no incentive to compromise on list price, offer a patient access scheme that would justify a NICE recommendation, or conduct further research.

Following its recent consultation the fund has proposed several reforms. It will introduce a rationing process that will use a more limited categorisation of the additional benefit (principally in terms of survival) and the cost (simply that of the drug) to prioritise the drugs on its list so that the fund remains within budget.[2] In other words, it will do a crude reassessment of the cost effectiveness of the drug—something that NICE has already assessed and found unacceptable. This process will continue to undermine NICE, duplicate effort, and distort allocation of NHS resources while failing to support the development of cost effective drugs from which patients could benefit.

A better prescription

A better process is needed. We propose that the fund should focus on those cancer drugs that may be cost effective but for which current evidence is insufficient. The process could be as follows:

- NICE considers new drugs as at present
- It identifies cancer drugs for which evidence is too uncertain for a positive recommendation but further research might show they are cost effective[3]
- These drugs are considered by a joint NICE-NHS England group that, with expert advice, decides whether at the manufacturer's price, further research is feasible and would justify its cost
- The group also decides whether in the meantime the drug should be generally available through the Cancer Drugs Fund or only to patients involved in the research
- When the research is complete, NICE would reappraise the evidence and decide whether the drug should now be recommended as cost effective
- If, as is likely, the number of drugs suitable for further research still exceeded the capacity for funding, prioritisation would be on the basis of the potential value to the NHS of the additional research.

As well as cancer experts, the joint NICE-NHS England group would need to include methods specialists, who could ensure that any proposed data collection obtained the maximum evidential value from using the drug. This evidence generation would need to be a serious and feasible exercise not simply an excuse to start using the drug.[4 5]

The fund would cover the costs of the drugs, with a flexible pricing agreement.[6] The additional costs of the research, which may be substantial, would need to come from other sources. The presumption should be that the manufacturer should fund and, where feasible, undertake the research because it is designed to show that the drug is cost effective at the company's price. Other possible sources of funding include the pharmaceutical industry through the rebated income from companies under the Pharmaceutical Price Regulation Scheme[7]; NHS funds allocated to research through the National Institute for Health Research, and other sources of funding intended to encourage pharmaceutical innovation. If the public sector funds the research, it would need to be clear how the NHS shares the return on that investment, which would obviously be linked to the price it pays for the products.

This would not be easy, and many details would need to be agreed. However, by helping to identify promising drugs for which more research could reduce the uncertainty about cost effectiveness, the Cancer Drugs Fund would support a rational revised process. This could prioritise the funding of cancer drugs to serve not just today's cancer patients but all patients seeking care from the NHS in the short and longer term.

Logically such a process should not be limited to cancer drugs, but if its value could be shown for cancer there is no reason why its remit and funding could not be extended in the future. The UK life sciences minister has just launched a "wide ranging review of the way new drugs and medical devices are developed and adopted in the UK"[8] with the intention of speeding up clinical trials and NHS patient access to new treatments. Such a review should consider an extended role for the process we suggest.

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Competing interests and references are on thebmj.com.

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thebmj.com

- Research: Leucocyte telomere length and risk of cardiovascular disease (*BMJ* 2014;349:g4227)
- Observations: Would you like your telomeres tested? (*BMJ* 2012;344:e681)
- Editorials: Will your telomeres tell your future? (*BMJ* 2012;344:e1727)

Mediterranean diet and telomere length

Genetic factors may contribute to the link between Mediterranean diet and longer telomeres

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Interest in telomere biology has increased in recent years, both because of the quest for a reliable marker of biological ageing and because shorter telomeres in leucocytes have been shown to predict coronary heart disease (CHD).[1 2] The methodological challenges of measuring telomere length have caused some delays in the progress of telomere research,[3] but strong genetic arguments exist in favour of a more causal association between abnormalities in telomere biology and CHD.[4] Most studies on the link between telomere length and disease remain cross sectional in design, so considerations of cause and effect are difficult. Observational research using repeated measurement of telomere length is needed to calculate the telomere attrition rate. The rate at which telomeres shorten is thought to be an even better biomarker of the ageing process than just measuring telomere length once.

A Mediterranean diet is the cornerstone of dietary advice in cardiovascular disease prevention, and the fact that it also links with a biomarker of slower ageing is reassuring

Genetic factors are important to our understanding of telomere biology and its role in risk of CHD, but we also know from many studies that lifestyle components are associated with both CHD risk and telomere length. For example, obesity, cigarette smoking, and consumption of sugar sweetened drinks have all been linked to shorter telomeres.[5 6]

In a new report from the Nurses' Health Study, Crous-Bou and colleagues found a positive association between increased adherence to a Mediterranean dietary pattern and longer telomeres in a subsample of 4676 disease-free women who completed extensive food frequency questionnaires and also had a blood test to measure telomere length in leucocytes.[7] However, none of the individual dietary components was associated with telomere length, underlining the importance of examining dietary patterns in relation to health, not just separate dietary factors such as intake of whole grains. The authors estimate that the difference in telomere length for each one point change in the Mediterranean diet score corresponded to 1.5 years of ageing, on average.

Still some unravelling to do

Extensive dietary assessment is one merit of this study, along with the well described methods for measuring relative telomere length using quantitative polymerase chain reaction. Limitations include the cross sectional design, the women only cohort, and the lack of any validation of their quantitative polymerase chain reaction method against Southern blot, accepted by some researchers as the gold standard method for measuring telomere length.[3]

This is a well studied cohort of professional women, but notably lacking is an analysis of cardiovascular events, most importantly CHD events, in relation to telomere length. Previous reports found that women more adherent to a Mediterranean diet were less likely to develop both CHD and stroke and also had moderately better cognitive function.[8 9] However, others found that telomere length was not associated with risk of ischaemic stroke.[10]

Higher plasma 25-hydroxyvitamin D concentrations have been linked to longer telomeres in this cohort,[11] along with increased physical activity.[12] Other studies have reported a moderate association between telomere length and both dietary patterns and body composition.[13] Links clearly exist between telomere length and women's lifestyles in the broadest possible sense.

From these reports, a picture emerges that middle aged American nurses prone to eat a Mediterranean diet and to be more physically active, with a more favourable body composition and better vitamin D metabolism, tend to have longer telomeres after adjustment for important confounders. Women with longer telomeres may have environmental factors in common, but they may also share certain genetic influences. It is not too great a leap to speculate that women preferring a Mediterranean diet might have an ethnic and cultural background in immigrant populations from the Mediterranean. A study in young men has previously shown geographical variation in telomere length across European populations, with young men from Naples, Italy, characterised by shorter telomeres than corresponding men from other corners of Europe.[14] On the other hand, older men in Crete, Greece, another south European population, have longer telomeres than Dutch men from Zutphen, the Netherlands.[15] This could reflect genetic factors regulating telomere biology in populations with different ancestry and age range. Sex differences in telomere biology may also exist, and as yet we have no similar comparative data on telomere length across countries in women.

Ethnic differences in telomere length have been documented in the United States.[3] This suggests a potential for genetic factors to explain at least some of the variation in self reported dietary intake and lifestyle, as ancestry and cultural influences could play an important role in both how we live our lives and how lifestyle preferences such as dietary patterns are developed.

The new report from the Nurses' Health Study adds to the evidence from the same female cohort that longer telomeres are associated with a cluster of beneficial characteristics of healthy lifestyles and possibly even better cognition. A Mediterranean diet is the cornerstone of dietary advice in cardiovascular disease prevention, and the fact that it also links with a biomarker of slower ageing is reassuring. Ideally, we need similar data in men, but also analyses on prediction of coronary events in relation to telomere length among these nurses.

Studies measuring the attrition or shortening of telomeres over time would add important new information to cross sectional analyses. Genetic background factors, reflecting ancestry, could probably explain some of the variation in the association between dietary patterns and telomere length, and future studies on this question should take into account the possibility of interactions between genes, diet, and sex.

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RESEARCH, p 12

thebmj.com

- Research: Development and validation of PRE-DELIRIC delirium prediction model for intensive care patients (*BMJ* 2012;344:e420)
- Clinical Review: Anticipating and managing postoperative delirium and cognitive decline in adults (*BMJ* 2011;343:d4331)
- News: Study of rivastigmine for delirium in intensive care is stopped after deaths (*BMJ* 2010;340:c2895)

Delirium on the intensive care unit

Deadly or not, delirium remains a serious threat to patients worldwide

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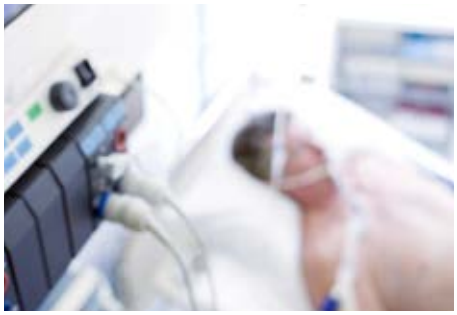
Over the past few years the interest in delirium in patients on the intensive care unit has gathered pace, seemingly exponentially. Given that delirium is common, particularly in ventilated patients, a recurring question is, "does delirium increase mortality directly or is it an epiphenomenon?" In a linked paper Klein Klouwenberg and colleagues try to answer this question.[1] In their prospective cohort study the authors used sophisticated statistical modelling to show that delirium probably does not increase mortality directly, overturning findings from a large body of previous observational research.[2 3]

Dealing with clinical situations that change over time (such as severity of illness) is one of the key challenges when exploring associations between delirium and death in critically ill patients. Traditional analysis methods may result in incorrect estimates if the main exposure (delirium) influences important covariates such as treatment decisions or clinical complications during follow-up, and also if the main exposure itself (severity of delirium) changes over time.[4] Both these problems occur in cohort studies linking delirium with mortality on the intensive care unit. Other complexities include the fact that patients who are discharged alive from intensive care may be in a different health state from those who remain on the unit (for whom further information is available), and that delirium preferentially develops in the most severely ill patients, who already have an increased risk of mortality.

Klein Klouwenberg and colleagues' analysed their data using both standard methods and a more sophisticated method, called a marginal structural model, which overcomes some of these difficulties. The different results illustrate clearly how inadequate adjustments can bias findings and may produce misleading conclusions. Once the analysis has been done correctly—adequately accounting for complex time varying relations between clinical conditions and the consequences and for the competing risks of discharge—the link between delirium and increased mortality disappears.



Now a top priority

Mortality has well known shortcomings as an outcome in studies on intensive care. In the 2014 BBC Reith lecture, "The Idea of Wellbeing," Harvard surgeon Atul Gawnde encourages a shift of focus from "mere survival" to protecting quality of life (www.bbc.co.uk/podcasts/series/reith). Delirium is essentially about the brain and is thought to increase the risk of long term cognitive impairment after critical illness, a concern for patients and their families.

The BRAIN-ICU trial enrolled 821 critically ill adults and assessed the global and executive function of survivors at three and 12 months after enrolment.[5] Twelve months after the critical illness, one in four patients had cognitive impairment comparable to mild Alzheimer's disease and one in three had impairment comparable to a moderate traumatic brain injury. The longer patients were delirious, the worse their cognitive outcome. This association with cognitive impairment may be subject to the same issues as mortality. However, the results of a sister study[6] in the same cohort showed no association between delirium and poor functional outcomes, suggesting the link with cognitive outcomes would not disappear if the data were analysed differently.

Cognitive impairment may follow

Delirium is a syndrome, not a diagnosis like smallpox. It is a constellation of signs and symptoms suggestive of a malfunctioning brain. Regardless of the cause, delirium is associated with neuroinflammation, alterations in blood flow, and electroencephalographic changes, indicating damage that could result in cognitive impairment. Neuroimaging studies are difficult to carry out on intensive care units, and rarely do patients have a baseline magnetic resonance image for comparison. However, researchers have reported an association between longer duration of delirium and smaller brain volumes[7] and between longer duration of delirium, white matter disruption, and later cognitive impairment.[8] Delirium alone may not directly cause death; however, ongoing pathological changes in the brain, manifested as delirium, cannot easily be dismissed.

Delirium in patients on the intensive care unit is at the extreme end of a spectrum of disease, and studies that exclude elective patients (27.8% of patients in Klein Klouwenberg and colleagues' study) may not generalise well to less intensive settings where patients have more reserve and less disease. Some interventions, for example, seem to decrease the risk of delirium in patients undergoing elective cardiac procedures but not of those admitted as emergencies to intensive care units.[9] Perhaps the burden of disease among emergencies is simply too great.

What does the future hold for research on delirium in critically ill patients? In the United Kingdom, the James Lind Alliance—a non-profit making organisation—brings together patients, carers, and doctors to ensure that funders invest in research questions that matter to patients and the professionals who care for them. A recent priority setting partnership with the UK Intensive Care Foundation started with a survey and review that generated over 1300 suggestions. After two years of work, the identification of delirium and how to monitor and manage its effects emerged as one of the top three priorities for research in intensive care.[10]

Many patients on the intensive care unit die with delirium. We now know delirium may not cause death directly but it does result in longer hospital stays,[1] complications, and anguish to patients, families, and carers in both homes and hospitals.[11-13] Good evidence suggests that many patients are left with delirium related cognitive impairment.

Delirium on the intensive care unit has now come of age. It may not be deadly, but it is still an extremely serious complication that richly deserves its priority status for action and research.

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RESEARCH, p 11

thebmj.com

- News: Insiders say NICE is being encouraged to be more favourable to industry (*BMJ* 2014;349:g6387)
- Research: Reporting of conflicts of interest from drug trials in Cochrane reviews (*BMJ* 2012;345:e5155)

Medical journals and industry ties

Zero tolerance on education articles with financial links to industry

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The BMJ was one of the first medical journals to seek declarations of competing interests from authors. Our focus is on financial competing interests as we believe these to be the most identifiable. We do, however, understand that competing interests come in many forms and we also routinely ask authors to declare relevant non-financial competing interests. The governing principle has been that transparency is a panacea.[1] We placed faith in this principle, but mounting experience and evidence tell us that we were only half right.[2] Transparency remains essential, but it isn't sufficient to eliminate bias or perception of bias.

We believe this risk of bias is particularly important for clinical educational articles that are designed to guide patient care. Recently we introduced more active management of competing interests, requiring authors to complete a more detailed declaration and excluding authors with close ties. Now we have decided to go a step further, as heralded three years ago.[3] From next year our clinical education articles will be authored by experts without financial ties to industry (box). By industry we mean companies producing drugs, devices, or tests; medical education companies; or other companies with an interest in the topic of the article. We are phasing in this policy to start with editorials, clinical reviews, and most practice series. We hope that by the end of 2016, this will have extended to the rest of our education section.

Why are we doing this? The first reason is that making clinical decisions based on information biased by commercial interests can cause harm, as happened with cardiotoxicity from rosiglitazone and rofecoxib.[5-7] We also believe that our educational content will have more impact if readers can trust it. We know that readers consider research papers written by authors with declared financial links to industry to be less important, relevant, rigorous, and believable[8 9]; they are also less willing to prescribe drugs evaluated in such papers.[9] Finally, we want to encourage a shift in the culture of medicine. We think that we can help to do this by promoting authors without financial ties to industry and offering them appropriate prominence and visibility.

Financial competing interests are endemic to the culture of medicine and are rarely driven by malign motives or actions. Our decisions not to proceed with an article or an author are not intended to pass judgment on an author's integrity. However, we cannot ignore the mounting evidence of systematic attempts by commercial interests to corrupt the literature and influence clinical decisions. Internal company documents revealed during litigation expose practices aimed at influencing clinicians such as funding medical meetings, dinners, studies, and articles.[10] Many clinical practice guidelines are little more than industry marketing tools because of the financial competing interests of their authors and sponsors.[11]

Making it work

Will our new policy mean we lose the expertise of those at the cutting edge of research? Are there enough experts free of industry ties to satisfy the needs of a weekly general medical journal? In some fields we may find it difficult to recruit authors free of relevant financial links with industry. But we believe the ethical arguments are persuasive and that this approach will cause less harm. We will study progress and report back. We are tracking how long and how many approaches it takes to find authors who are free of financial links. We are willing to miss out on articles on a few topics in exchange for publishing more articles by authors with no relevant financial ties to industry. And things should become easier over time: if current trends continue then ties between academics and industry are on the wane.[12] We will let you know about the topics we struggle with, which in itself will be educational.

We realise that non-financial influences matter.[13] However, our aim is not to eradicate all competing interests—that would be impossible. Nor do we want to be anti-business just for the sake of it. Rather we wish to focus on ties that are known to, and indeed are largely designed to, influence clinical decisions in favour of industry.

We can also learn from the experience of other journals. In 2002, the *New England Journal of Medicine* abandoned a strict policy on authors with industry ties. "Our ability to provide comprehensive, up-to-date information, especially on recent advances in therapeutics, has been constrained," conceded its editors.[14] However, an editor in chief of *NEJM* when that policy operated in the 1990s explained how it could be made to work.[15] For over two decades the journal *American Family Physician*, which primarily publishes clinical reviews, has not considered articles by authors who have financial ties with industry.[16]

Please let us have your views on this change in *The BMJ*'s editorial policy. Our aims are to preserve and enhance readers' trust in the journal's content and to help to shape a new relationship between journals and industry, rather than perpetuate the perception of medical journals as the marketing arm of commercial interests.

Competing interests and references are on thebmj.com.

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Competing interest definitions and process for *The BMJ*'s editorials and education articles (including clinical reviews, practice articles, and state of the art reviews)

"A conflict of interest arises when a person has a personal or organisational interest that may influence or appear to influence the work they are doing. Usually this is a financial interest, but it may also be non-financial."[4]

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- Each author's declaration is carefully assessed by the handling editor, and may be discussed at a regular editors' meeting, to ensure our decisions are consistently and fairly applied by the editorial team.
- We have started publishing authors' competing interests forms alongside the articles, and advise authors of this when they send their forms. We plan to do so for all editorials and education articles
- From 2015, we will roll out a policy of editorials and clinical education articles authored by experts without financial ties to industry (companies producing pharmaceuticals, devices, or tests; medical education companies; or other companies with an interest in the article topic)