EDITORIALS

Editorials are usually commissioned. We are, however, happy to consider and peer review unsolicited editorials
See http://resources.bmj.com/bmj/authors/types-of-article/editorials for more details

bmj.com Observations: Online health checks may obscure effective advice (*BMJ* 2012;345:e6745)

The value of conducting periodic health checks

Scant evidence to show that they reduce morbidity and mortality in adults

Domhnall MacAuley primary care editor, *BMJ*, London WC1H 9JR, UK dmacauley@bmj.com

Routine health checks or periodic health examinations, a term used in North America, are seductive. They seem sensible. If prevention is better than cure then they seem a socially responsible approach to caring for patients. Doctors, politicians, and the public buy into the idea that a systematic routine check can identify health problems at an early stage and put them right. A body maintenance programme—like a vehicle service to ensure we are roadworthy—sounds like a good idea. But not every good idea stands up to critical appraisal.

In a linked systematic review and meta-analysis, Krogsbøll and colleagues comprehensively searched for randomised controlled trials that examined the effectiveness of health checks in adults in reducing morbidity and mortality.[1] Carried out according to the exacting methodological standards of the Cochrane Collaboration, the review analysed data from 14 trials with a variety of interventions and outcomes in different settings.[2] The authors found no evidence that general health checks made any difference to any of the studied outcomes. They also concluded that such health checks might increase overdiagnosis.

These findings are important for general practice in many countries. Furthermore, health checks are also promoted beyond primary care services, by private clinics, and by industry, where some companies support initiatives to improve employees' health. The current study carries a useful message for those who create national policy—that such initiatives are ineffective and probably a waste of resources. The original research included in the review comes from many countries with different health systems. Even in countries where health insurance funds care the findings support a clear message to insurers.

What are the limitations of this review? Some of the studies are old and perhaps not as immediately relevant as they once were. There is also considerable heterogeneity between the studies. The interventions took place in several countries, involved different healthcare professionals, and had different outcomes. Some were based in primary care but others were in different settings. Critics might argue that it was inappropriate to gather all these

trials together in one meta-analysis. In some trials participation rates were less than ideal, which may reflect the reality of practice. Implementation of interventions within the trials may have been suboptimal, but we cannot tell because details of individual trials cannot be scrutinised. Could it be that follow-up wasn't long enough to show whether the health check interventions made a difference? This is possible, but the mean duration of the studies suggests that it is unlikely. We should maintain a degree of circumspection in view of the wide confidence intervals, however.

The most interesting question is whether health checks do harm. People may gain inappropriate reassurance from a verdict of a "clean bill of health," which may lead to continued risky behaviour. A false positive test result may cause considerable worry and upset, not to mention inappropriate treatment. A false negative result also provides inappropriate reassurance. The availability of the routine health check may also divert patients from presenting appropriately with symptoms, signs, or complaints of concern, leaving it up to the doctor or health check to discover the problem. Furthermore, resources may be diverted from diagnosis and treatment to ineffective anticipatory care. Krogsbøll and colleagues found, for example, that health checks increased the diagnosis and treatment of hypertension but with no improvement in outcomes, which, they concluded, suggested overdiagnosis and overtreatment.

Not every good idea stands up to critical appraisal

When the Oxford and Collaboration Health Check (OXCHECK) and British Family Health studies, which evaluated regular health checks delivered by nurses, were published in the 1990s they stimulated considerable debate.[3 4] They showed that scheduled medical examinations led to small changes in cardiovascular risk factors, but there was no consensus on whether it was worth the considerable effort and expense in running these nurse led clinics.

In their review of the cost effectiveness of these studies, Wanderling and colleagues pointed out that the mean number of life years gained per person screened from the British Family Heart Study ranged between 0.0062 (assuming a one year effect) and 0.2035 (assuming a 20 year effect) for men and between 0.0011 and 0.0626 for women.[5] The mean number of life years gained from the OXCHECK study ranged between 0.0034 (assuming a one year effect) and 0.1093 (assuming a 20 year effect) for men and between 0.0018 and 0.1065 for women. In a *BMJ* editorial,[6] Nigel Stott discussed the findings of these two studies, pointing out that the health check approach through primary care alone would not produce large reductions in the risk of cardiovascular disease. He called for more effective legislation on controlling the use of tobacco and promoting the consumption of healthy food instead, messages that remain important today.

The current study finds that regular health checks are ineffective. It robustly shows evidence of little effect. It remains possible that targeted health checks might offer some benefit. This study looks at health checks in well people only, and initiatives that are focused on particular population groups with identifiable risk factors and conditions could possibly be effective, but evidence of this is needed. The history of health promotion through routine health checks has been one of glorious failure, but generations of well meaning clinicians and public health physicians struggle to allow themselves to believe it. We need to reinforce the message lest some enthusiast reinvent the health check in another guise. Policy should be based on evidence of wellbeing, rather than on well meant good intentions.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2012;345:e7775

RESEARCH, p 14

A structured approach to care is a key component of effective strategies to reduce blood pressure

The use of highly structured care to achieve blood pressure targets

Computer support helps, but lower targets may not be achievable or cost effective in primary care

Christopher E Clark clinical academic fellow, Primary Care Research Group, Institute of Health Services Research, University of Exeter Medical School, Exeter EX1 2LU, UK
christopher.clark@pms.ac.uk
Richard McManus professor of primary care, Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Hypertension is a major risk factor for premature morbidity and mortality throughout the world.[1] In 2010 the prevalence of hypertension in the health survey for England was 32% in men and 29% in women.[2] Hypertension is a common reason for consultation in primary care, and blood pressure is a key indicator within the UK Quality and Outcomes Framework.[3] Although the "rule of halves" (half of people with hypertension are undetected, half of those detected are not treated, and in half of those treated hypertension is not controlled) was published 40 years ago,[4] the problem of suboptimal control of high blood pressure remains. Reviews have identified that a structured approach to care is a key component of effective strategies to reduce blood pressure.[5 6]

In a linked paper, Stewart and colleagues present the findings of a large trial of structured care that used a computerised algorithm to titrate antihypertensives to target blood pressure.[7] The trial was conducted in primary care, where most patients with hypertension are treated,[2] and recruited from a range of practices across almost the entire continent of Australia. Participants were adults with new and established hypertension whose blood pressure remained above target after stopping any current antihypertensive drugs and a 28 day run-in period during which they received 80 mg valsartan daily. Almost a third were excluded after the run-in period, mostly because their blood pressure was adequately controlled. This study therefore looked at patients with hypertension who were not controlled by treatment with an angiotensinogen receptor blocker (ARB).

Eligible participants were then set individualised blood pressure targets, using computer support, according to their cardiovascular risk assessment at entry: 125/75 mm Hg in the presence of proteinuria, 130/80 mm Hg in the presence of target organ damage, or 140/90 mm Hg if neither of these were detected. They were then randomised to usual care with treatment over and above ARB determined by their general practitioner or to an intervention. The intervention used an intensive algorithm based blood pressure management strategy with computer support, and it was designed to achieve the patient's target blood pressure within six months. Within the intervention group participants were further randomised to monotherapy with ARB or dual therapy with the addition of a diuretic or calcium channel blocker.

Significant pooled reductions in blood pressure were seen in both groups (13.2/7.7 mm Hg for the intervention and 10.1/5.5 mm Hg for usual care), with the primary outcome measure of achievement of target in favour of the intervention (36.2% *v* 27.4%). This difference in primary outcome was significant only for those with blood pressure targets above 125/75 mm Hg. Prescription rates and drug side effects for combinations of treatments were greater in the treatment arm, which suggests some success in overcoming clinical inertia.[8]

Cautious interpretation of the findings is warranted. Participants were relatively young (mean age 58 years), but only 40% had uncomplicated hypertension. The authors carefully describe "usual care," which was enhanced by clinical profiling and target setting at study entry.[9] Outcome blood pressure measurements for participants were obtained for pragmatic reasons by the GPs or nurses delivering the intervention using an unblinded protocol. This is a source of bias in studies of this type, and independent assessment would have been preferable.[10] "Aberrant" blood pressure readings were discarded and included those with a greater than 10 mm Hg difference between systolic blood pressure readings, which is less than the mean difference between first and third readings seen in a recent Canadian study using automated sphygmomanometers.[11] Participants randomised to the intervention were seen twice as often as those receiving usual care; therefore, the omission of an associated cost effectiveness analysis is important if such a strategy is to be implemented on a wider scale.

The authors of this industry sponsored study describe the initial intervention (valsartan) as one of the most commonly prescribed antihypertensive agents globally. It is, however, an alternative first line agent only for people under 55 years of age in the UK.[12] The more stringent blood pressure targets in this study are lower than those advised by the National Institute for Health and Clinical Excellence, and they are arguably lower than current evidence suggests other than for stroke.[12 13] Despite 14% of participants in each group being assigned blood pressure targets higher than computer recommendations at the GP's discretion, there was still evidence of deviation from the study protocol because GPs failed to up-titrate treatment for the more stringent blood pressure targets. More withdrawals and twice as many adverse events occurred in the intervention group. Given that performance is likely to be worse outside of trial conditions, achievement of aggressive blood pressure reduction may not be realistic, and may even be inadvisable, for many patients.

This study demonstrates the potential returns from computer aided structured care for the management of high blood pressure and how it could be delivered across a large geographical area. We now need to understand whether these effects depend on the choice of drug, how cost effective such interventions are, and which groups would benefit from the more stringent targets used in this study.

Competing interests: None declared.
Provenance and peer review: Commissioned; not externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2012;345:e7777

RESEARCH, p 15

bmj.com

- Editorial: Safety of tiotropium (*BMJ* 2011;342:d2970)
- Research: Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease (*BMJ* 2011;342:d3215)

Call for worldwide withdrawal of tiotropium Respimat mist inhaler

Tiotropium Respimat mist inhaler increases the risk of death

Richard Beasley professor of medicine, Medical Research Institute of New Zealand, Wellington, New Zealand
richard.beasley@mrinz.ac.nz
Sonal Singh assistant professor of medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA
Yoon K Loke senior lecturer in clinical pharmacology, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK
Paul Enright professor of medicine (retired), College of Public Health, University of Arizona, Tucson, AZ, USA
Curt D Furberg professor emeritus, Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA

DR P MARAZZI/SPL

Use of the Respimat device confers greatest risk

Ten years ago serious concerns were raised about a link between inhaled anticholinergics and an increased risk of serious cardiovascular events and death in chronic obstructive pulmonary disease (COPD).[1] Since then our understanding has grown about the effects of individual formulations of anticholinergic drugs and about their effects in patients with COPD and comorbidities. We believe that evidence of increased mortality from cardiovascular disease and all cause mortality with the tiotropium Respimat mist inhaler is now so strong that this inhaler should be withdrawn from the market.

In 2002, a randomised placebo controlled trial showed that regular use of ipratropium by metered dose inhaler increased the risk of death from cardiovascular disease (relative risk 2.57, 95% confidence interval 1.12 to 6.62).[1] In 2008, a systematic review and meta-analysis of 17 randomised controlled trials of ipratropium and tiotropium (13 645 patients) reported an increased risk of the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke (1.60, 1.22 to 2.10).[2] It also reported increased risks of myocardial infarction (1.52, 1.04 to 2.22) and cardiovascular death (1.92, 1.23 to 3.00) but not stroke (1.46, 0.81 to 2.62).[2] The relative risk for the primary composite endpoint was 1.70 (1.19 to 2.42) for ipratropium and 1.49 (0.98 to 2.26) for tiotropium.

Later in 2008, reassurance was provided with publication of the industry sponsored randomised placebo controlled UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial of 5993 patients. This trial found no increased risk of mortality (hazard ratio 0.89, 0.79 to 1.02) or myocardial infarction (relative risk 0.73, 0.53 to 1.00) with tiotropium (Spiriva Handihaler).[3] However, patients with coexisting illnesses were excluded, such as those with moderate to severe renal impairment (which doubles plasma tiotropium concentrations[4]), a recent history of myocardial infarction, unstable or life threatening cardiac arrhythmia, or admission for heart failure.[3 5] These exclusions limited the generalisability of the safety findings and of the overall results to unselected patients with COPD, many of whom also have cardiovascular or renal disease.[6] The reduction in COPD exacerbations and modest improvement in lung function and quality of life contributed to the favourable risk-benefit profile of tiotropium reported by this study.[3]

However, in 2011 a systematic review and meta-analysis of randomised placebo controlled trials of tiotropium delivered by the new Respimat mist inhaler device reported significantly increased risks of all cause mortality (relative risk 1.52, 1.06 to 2.16) and cardiovascular death (2.05, 1.06 to 3.99).[7] The findings raised the possibility of a dose-response effect on all cause mortality, with relative risks of 1.46 (1.01 to 2.10) and 2.15 (1.03 to 4.51) with the 5 µg and 10 µg preparations, respectively.[7] It was not possible to determine whether the risk of death was associated with duration of treatment because there were too few studies. Importantly, in the largest Respimat study, risk of death from cardiac disease was most notably increased in patients with known cardiac disease or rhythm disorders (relative risks 4.03 (1.15 to 14.13) and 8.61 (1.10 to 67.2), respectively).[4 5]

In 2012, a Cochrane review of tiotropium versus placebo for COPD confirmed the significant increase in mortality for tiotropium Respimat (Peto odds ratio 1.47, 1.04 to 2.08).[8] Subgroup analysis found a significant difference between the studies using the Handihaler and Respimat inhalers (test for subgroup differences P=0.01). This differential risk may result from greater systemic exposure with the Respimat device than with the Handihaler.[9 10]

Consistent with the Cochrane review,[8] an independent systematic review and mixed treatment comparison meta-analysis of randomised controlled trials of drugs used in COPD confirmed that tiotropium Respimat increased the risk of death compared with placebo (odds ratio 1.51, 1.06 to 2.19) and with other inhaled drugs, including tiotropium Handihaler (1.65, 1.13 to 2.43), long acting β agonists (1.63, 1.10 to 2.44), and a combination of corticosteroids and β agonists (1.90, 1.28 to 2.86).[11] The risk was greatest for death from cardiovascular disease, in patients with severe COPD, and at a higher daily dose. The generalisability of these findings is supported by a recent analysis from a Dutch general practice database, which showed that the use of tiotropium Respimat in clinical practice increased the risk of death (hazard ratio 1.52, 1.28 to 1.87), an association which remained after adjustment (1.33, 1.07 to 1.65).[12]

Clearly, more placebo controlled safety studies of anticholinergic inhalers in patients with comorbid conditions are needed. But, for now, the case for withdrawing tiotropium Respimat is compelling. We see no justification to expose patients to a drug for which one excess death can be expected for every 121 patients treated with the 5 µg dose for 12 months,[13] when a preparation with similar efficacy and less harm is available. The proposed benefits of the Respimat device—that it is simple to use and that the delivered dose is independent of respiratory effort—are unlikely to be clinically relevant when the Respimat and Handihaler devices have similar efficacy.[14] Although tiotropium Respimat is not approved for use in the United States, it remains available in the United Kingdom and at least 54 other countries. Warnings are not enough to protect patients; withdrawal would align all regulatory authorities with the current position of the US Food and Drug Administration. Thus we call for the immediate worldwide withdrawal of the tiotropium Respimat mist inhaler.

Competing interests: None declared.
Provenance and peer review: Not commissioned; externally peer reviewed.
References are in the version on bmj.com.
Cite this as: *BMJ* 2012;345:e7390

It is no longer possible to pretend that a report of a clinical trial in a medical journal is enough to allow full independent scrutiny of the results

The new *BMJ* policy on sharing data from drug and device trials

Is a necessary next step towards the full sharing of all anonymised trial data

Fiona Godlee editor, *BMJ*
Trish Groves deputy editor, *BMJ* tgroves@bmj.com

Last month the *BMJ* announced a new policy on sharing data from clinical trials.[1] From January 2013, trials of drugs and medical devices will be considered for publication only if the authors commit to making the relevant anonymised patient level data available on reasonable request. This new policy will apply to any paper that reports the main endpoints of a randomised controlled trial of one or more drugs or medical devices in current use, whether or not the trial was funded by the industry (box).

Why the new policy? Because it is no longer possible to pretend that a report of a clinical trial in a medical journal is enough to allow full independent scrutiny of the results. Journals are, of course, not the only potential channel for such scrutiny, but as long as publication remains the main currency for academic recognition, journals have a responsibility to use what power they have to push for greater transparency. If research is to help doctors and patients make the best clinical decisions, it must be reliable and reproducible. These are qualities that current peer review processes cannot assure.

Since announcing the new policy we have been asked why it applies only to trials of drugs and devices, what is meant by "relevant," and who will judge whether a request is "reasonable." We have started with drugs and devices as being the areas of medicine where most evidence exists for incomplete and misleading trial publication, but we expect that the policy will be extended to cover all clinical trials. "Relevant data" encompasses all anonymised data on individual patients on which the analysis, results, and conclusions reported in the paper are based. As for "reasonable request," the *BMJ* is not in a position to adjudicate, but we will expect requesters to submit a protocol for their re-analysis to the authors and to commit to making their results public. And we are at least able to make the transaction transparent. We will encourage those requesting data to send a rapid response to bmj.com describing what they are looking for. If the request is refused we will ask the authors of the paper to explain why.

Does the new policy represent a big change? The extensive media coverage would suggest so.

To which papers does the *BMJ* policy apply?

We hope that authors will be inclusive rather than parsimonious when committing to make data available. The *BMJ* policy applies to papers reporting studies with these characteristics:

- Clinical trials
- Main endpoints—Pre-specified primary outcome(s) and harms
- Drug—This means a medicinal product for human use.
- Medical device— Our policy is aimed most squarely at what the US Food and Drug Administration calls class III devices. Examples include pacemakers, stents, and prostheses.

The *BMJ* policy does not currently apply to trials of diagnostic tools or surgical operations or of any other interventions that are not drugs or devices.

The policy applies to papers submitted from January 2013, regardless of when the trials were conducted and regardless of the sources of funding and sponsorship for the trial.

But we see it as just one step up from our current policy: since 2009 we have encouraged authors to share their data on request and have required them to say whether they will or not. The results across the *BMJ* and *BMJ Open* have been promising: many of our authors now say that they will share their data on request, and one *BMJ*[2] and 23 *BMJ Open* papers have datasets posted on Dryad, the digital repository with which we have partnered (http://datadryad.org). A survey of triallists published in the *BMJ* this week gives further cause for optimism. Joe Ross and colleagues emailed 683 corresponding authors of trials published in the six major general medical journals. About three quarters of the 317 who responded said that they thought data sharing through data repositories should be required, and a similar proportion said that data sharing should be required in response to individual requests.[3]

But the *BMJ*'s new policy has clear limitations and is by no means the end of the story. The *BMJ* publishes relatively few trials of drugs and devices. Of the 226 research papers published so far this year, 31 were the main reports of randomised controlled trials, of which most were trials of health services. Six trials were of drugs, none were of devices, and only one of the drug trials was sponsored by industry.[4] The *BMJ*'s new policy is a signal, but it won't change things on its own. The *Annals of Internal Medicine* and *PLoS Medicine* both have policies on data sharing.[5 6] We hope that other journals will follow, and we look to the International Committee of Medical Journal Editors, of which the *BMJ* is a member, to take a decisive lead.

But because many trials never get published in journals at all,[7] real change will come only when the regulators raise their game. Here too there is scope for optimism. After pressure from the Nordic Cochrane Centre,[8] the European ombudsman ruled that the European Medicines Agency had been wrong to hold clinical trial data as commercial in confidence. The agency's new director, Guido Rasi, responded by announcing earlier this year that the agency would publish clinical trial data once a drug has been approved.[9] A workshop this week aims to hammer out the details.[10]

If patient anonymity is assured, the most efficient and effective option must be open deposition of patient level data plus the underlying code and background documentation. However, all the signs are that the initial approach will fall short of this ideal, with a focus instead on availability on request. Contracts will therefore need to be agreed between data "owners" and "requesters." This is not straightforward, as illustrated by negotiations with GlaxoSmithKline over data on its neuraminidase inhibitor zanamivir (Relenza) (bmj.com/tamiflu) and by the Yale University open data access project and its critics.[11 12] The European Medicines Agency will also fall short of expectations if it does not extend its commitment retrospectively, to encompass data on older drugs still in current use. The oseltamivir (Tamiflu) saga suggests that opening up historical datasets will be as important to patient care and healthcare budgets as anything done prospectively.[13]

There are many complex issues to resolve as we move into a brave new world of open trial data. Progress on some of these may seem painfully slow. And with success will come other challenges: this new breed of re-analyses must be held to account as rigorously as the originals. But we are several steps nearer to our immediate goal: proper independent scrutiny of the trial data for all drugs and devices in current use.

Competing interests: None declared.

References are in the version on bmj.com.

Cite this as: *BMJ* 2012;345:e7888