MANCHESTER’S BUDGET CONTROL

Where Manchester leads
London should follow

The plan to pass control of the entire health and social care budget of £66bn (£8.3bn; €8.7bn) a year to Greater Manchester local authority is bold, innovative, and exciting. ¹ It is a landmark on the NHS’s route towards a holistic integrated service that unites health and social care.

But what is good for Manchester is also urgently needed in London. London faces a high burden of illness (both physical and mental), health inequalities remain stubbornly widespread, and quality of care is variable.

The London Health Commission (www.londonhealthcommission.org.uk), which I chaired, recommended last October a switch from care focused around the NHS to care focused around Londoners—groups of similar people with similar needs. This might be quick convenient care (professionals in work), continuity of care and a focus on social needs (older people), or care that comes to them (people with intensive needs).

To achieve this, we need more joint teams in the community, more joined up working, and more integration between health and social care. Running health and social care separately no longer makes sense. The current arrangement creates confusion, perverse incentives, and distress for people trying to navigate an NHS that is free at the point of use and a social care system that is heavily needs and means tested.

London has a history of successful change, as illustrated by its radical reform of specialist stroke services, which now deliver a 30 day mortality rate 17% below the average in England. Manchester’s leaders are to be congratulated on seizing the initiative and negotiating this historic deal to reform care in their great city. London’s leaders should not dally, but follow swiftly in their path.

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¹ Iacovou C. Manchester authority is set to take control of £66bn worth of health and social care spending. BMJ 2015;350:h1110. (26 February)

Cite this as: BMJ 2015;350:h1572

WASTAGE IN CLINICAL TRIALS

Journals have role in checking timing of trial registration

Clinical trial registration is pivotal to understanding the research landscape and for ensuring research accountability. But what do we do when protocols to ensure public access to information are in place but chains of responsibility fail?

Prospective clinical trial registration is mandated by the International Committee of Medical Journal Editors’ (ICMJE) uniform requirements for manuscripts as a pre-condition for publication. ¹ Prospective registration limits selective outcome reporting. However, the chain of accountability cannot end with trialists—journal editors must also ensure compliance with ICMJE registration mandates.

Increasingly, registries allow retrospective trial registration, so reporting of registry numbers is no longer proof that trials are registered in accordance with ICMJE mandates. As such, journal editors should confirm the timing of registration.

A Pan African Clinical Trials Registry (www.pactr.org) study examined 68 randomised controlled trials published from October to December 2011. Three trials provided no trial registry information. Of 36 retrospectively registered trials, 21 registered after July 2005, and therefore published in conflict with the ICMJE prospective registration amnesty. Fourteen trials reported different primary outcomes from those in the registry.

What are the implications? Clinical trial publication offers journals “opportunities to accrue citations, influence, and reprint orders,” ² so commercial interests could receive precedence over the ethical responsibility of transparency in science. Equally plausible is that editors do not realise that registries accept retrospective registration. Members of WHO’s network of registries flag retrospectively registered trials, but other registries do not. The onus rests with editors to check registration timing. International research governance protocols will succeed only if the highest standards of responsibility and accountability are required from all.

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Cite this as: BMJ 2015;350:h1436

WARFARIN AND ATRIAL FIBRILLATION

Problems with using numbers needed to harm

I have some questions about Jun and colleagues’ use of number needed to harm in their research article on the association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment. ³

In the methods they wrote: “Based on the adjusted incidence rates of major bleeding in chronic kidney disease (defined as <60 mL/min/1.73 m²) and non-chronic kidney disease (<60 mL/min/1.73 m²), we determined the number needed to treat to harm.” In the results section they wrote: “Among participants with chronic kidney disease, the number needed to treat to harm was 22 (95% confidence interval 18 to 27) during the first 30 days of warfarin treatment.”

These figures seem quite alarming, given the number of patients who have atrial fibrillation and an estimated glomerular filtration rate (eGFR) <60. However, it seems that they derived their number needed to harm from the excess in incidence rate among those with an eGFR <60 versus those with an eGFR ≥60. Surely, isn’t this the number needed to harm for inducing chronic kidney disease in patients with atrial fibrillation on warfarin? Shouldn’t the number needed to harm of warfarin therapy be calculated on the basis of a comparison with a control group that did not take warfarin?

More generally, I wonder if the authors should be reporting number needed to harm at all. Data on crucial confounders such as smoking are lacking, there is no comparison with a control group or with the baseline pre-warfarin hazard of the study participants.
themselves, and those at highest risk would not have been started on warfarin in the first place. The authors correctly never make an outright causal claim because this could not be sustained. However, doesn’t calculating a number needed to harm implicitly involve make a strong causal assumption?

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According to our use of the number needed to treat to harm (NNH), we aimed to determine the impact of chronic kidney disease on the risk of major bleeding in older adults with atrial fibrillation, specifically those starting warfarin.

We focused on assessing the risk of major bleeding in these patients because reluctance to use warfarin mostly relates to uncertainties about its safety in this setting, and data on its use at different stages of chronic kidney disease are limited. As such, we used the non-chronic kidney disease group (estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m²) as the “control” group to calculate the NNH. In other words, among patients with atrial fibrillation starting warfarin, for every X number of patients with chronic kidney disease (eGFR <60 mL/min/1.73 m²), one patient would experience a major bleeding (safety of warfarin therapy) in older adults with atrial fibrillation, specifically those starting warfarin.

However, we acknowledge that when assessing the rate (eGFR) ≥60 mL/min/1.73 m²) as the “control” group to calculate the NNH. In other words, among patients with atrial fibrillation starting warfarin, for every X number of patients with chronic kidney disease (eGFR <60 mL/min/1.73 m²), one patient would experience a major bleeding event, compared with patients without chronic kidney disease. This allowed us to assess the impact of chronic kidney disease on the risk of bleeding in patients with atrial fibrillation who were starting warfarin when estimating absolute measures of treatment effects that are clinically meaningful.

The substantial difference in the NNH during the first 30 days of warfarin compared with the period after highlights the need to consider bleeding risk relative to kidney function, particularly shortly after warfarin is started. However, we acknowledge that when assessing NNH in this way, the increased risk of major bleeding with worsening kidney function in patients starting warfarin should be balanced against the risk of stroke according to chronic kidney disease status. However, according to the above rationale, we focused on the safety of warfarin in new users.

As Williams pointed out, on the basis of our current data, we do not (and cannot) assert that warfarin “causes” major bleeding in patients with chronic kidney disease and atrial fibrillation. To postulate a causal association between warfarin and clinical outcomes in patients with atrial fibrillation (by different levels of kidney function), the risk of stroke and major bleeding must be assessed in warfarin exposed and unexposed groups, ideally in a randomised controlled trial.

Regarding our use of the number needed to treat to harm (NNH), 1 2 we aimed to determine the number needed to treat to harm (NNH) in this way, the increased risk of major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. BMJ 2015;350:h246. (3 February)

Cite this as: BMJ 2015;350:h1581

Authors’ reply

QUETIAPINE AND MAJOR DEPRESSION

Severe adverse reactions associated with quetiapine

Over the past 20 years the use of second generation antipsychotics has shifted from schizophrenia to affective disorders. Pringsheim and colleagues described the benefits and risks of quetiapine as adjunctive treatment in major depressive disorder. 1 However, they did not mention some of the severe adverse reactions associated with quetiapine.

One such problem is QTc prolongation, especially when combined with other drugs, 2 and an odds ratio of 0.17 compared with placebo has been reported. 1 Although the risk of increased concentrations of prolactin seems small, gynaecomastia and galactorrhoea have been reported. 3 Another problem is that quetiapine may lower the seizure threshold (incidence of 1% to 10%). 2 4 In addition, an association with serotonin syndrome has been reported, as have severe withdrawal symptoms. 5 Quetiapine is metabolised by cytochrome P450 3A4 into more than 20 (active) metabolites. Clinical pharmacokinetic and pharmacodynamic interactions must be considered in patients with major depressive disorder on combination therapy.

The risk-benefit analysis of adjunctive treatment with quetiapine is based on many factors. Decisions must be made on an individual basis, taking strength and duration of major depressive disorder, the patient’s age and comorbidities, other drugs (such as antidepressants, mood stabilisers), and treatment costs into account.

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Cite this as: BMJ 2015;350:h1582

Cite this as: BMJ 2015;350:h1576

Authors’ reply

Rivers discusses the application of insect repellents to the face. 1 2 Application of a repellent to the face may not always be needed because mosquito bites occur mainly on other parts of the body—for example, around the feet and ankles with Anopheles gambiæ, the main malaria vector. Bites on the face are often avoided because people tend to notice mosquitoes landing on their face and defend themselves before the bite occurs. However, travellers who think that they are at risk of being bitten on the face can wear repellent if the instructions on the bottle allow it.

We agree that the repellent should be sprayed onto the hands first and then applied carefully to the face to prevent accidental ingestion. Parents should apply the repellent to children.

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Cite this as: BMJ 2015;350:h1577

MOSQUITO REPELLENTS FOR TRAVELLERS

Application of insect repellents to the face

Stanczyk and colleagues provide a good overview of topical insect repellents. 1 However, by recommending that insect repellent should not be applied to the face, they are leaving travellers with up to 5% of their total body surface area free to mosquito and insect bites, with potentially devastating effects.

The US Environmental Protection Agency states that insect repellent can be applied to the face but should not be applied around the eyes or mouth, and only sparingly around the ears. 2 When advising patients how to apply insect and mosquito repellents, doctors should tell patients to spray the repellent onto their hands first and then apply it carefully to the face to prevent accidental ingestion.

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Cite this as: BMJ 2015;350:h1576

Cite this as: BMJ 2015;350:h1577