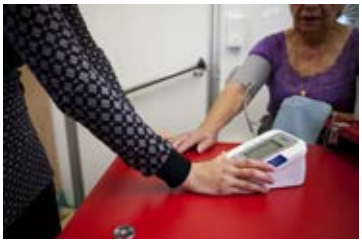
research

Compliance with EU Clinical Trials Register is poor p 311



Intensified BP treatment for older adults at hospital discharge p 312

Folic acid after first trimester does not prevent pre-eclampsia p 314

ORIGINAL RESEARCH Cohort study and web resource

Compliance with requirement to report results on the EU Clinical Trials Register

Goldacre B, DeVito NJ, Heneghan C, et al

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Find this at: http://dx.doi.org/10.1136/bmj.k3218

Study questions Have universities and drug companies complied with new EU rules requiring them to report all trial results directly on to the EU Clinical Trials Register (EUCTR), for all trials conducted in Europe since 2004? And is it possible to create a live audit tool for compliance?

Methods The authors downloaded the EUCTR and applied appropriate filters to identify all trials that were required to report results. They assessed overall compliance and conducted regression analyses to assess whether certain types of trial were more or less likely to report results. Beyond reporting a single set of overall compliance rates, the authors also set out to produce a live, openly accessible online resource—with regularly updated data—to provide compliance statistics for every individual university and company, and to give the reporting status of every individual trial.

Study answer and limitations 7274 trials were due to report results on to the register, yet only 49.5% (n=3601) had done so. Trials with a commercial sponsor were substantially more likely to post results than those with a non-commercial sponsor (68.1% *v* 11.0%). Several trials on the register had missing or inconsistent data and it is likely that this led to an over-estimation of compliance. The online tool was created successfully (see EU.TrialsTracker.net for current compliance data on all individual trials and sponsors).

What this study adds Compliance with the European Commission requirement for all trials to post results on to the EUCTR within 12 months of completion has been poor, with half of all trials non-compliant. Accessible and timely information on the compliance status of each individual trial and sponsor, from the online tool, may help sponsors prioritise and improve reporting rates.

Truncated screenshot of single sponsor page on EU.TrialsTracker.net

Funding, competing interests, data sharing
This work was funded by a grant from the Laura and John Arnold Foundation to BG to work on problems in clinical trial reporting. BG and CH are cofounders of the AllTrials campaign to improve trial reporting. All data and code are shared openly online.

Managing blood pressure medication at discharge

ORIGINAL RESEARCH National retrospective cohort study

Intensification of older adults' outpatient blood pressure treatment at hospital discharge

Anderson TS, Wray CM, Jing B, et al

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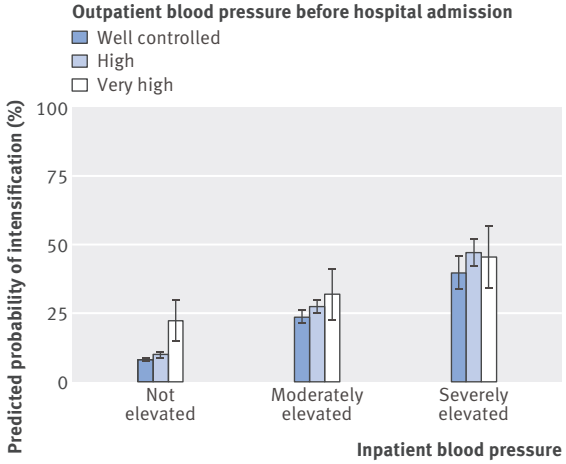
Study question How often are older adults discharged from hospital with intensified antihypertensive drug regimens?

Methods This was a retrospective cohort study of older adults (≥65 years) with hypertension who were admitted to hospital for non-cardiac conditions in the US Veterans Administration Health System between 2011 and 2013. The frequency of patients receiving intensified antihypertensives at hospital discharge, defined as a new antihypertensive or a higher dose antihypertensive, was examined along with patients' characteristics associated with the likelihood of receiving intensified antihypertensive treatment.



Predicted probability (95% CI) of intensification of antihypertensive treatment by inpatient and outpatient blood pressure. Predicted probabilities estimated following mixed effect logistic regression

COMMENTARY What happens in hospital, stays in hospital

Discharge from hospital is an especially high risk transition for older adults. Despite recovery from the condition for which they were admitted, many patients are discharged with a functional status that is substantially worse than their pre-admission baseline.[1] Recently, increasing attention has been paid to this problem, including the generalised period of risk immediately after discharge now known as post-hospital syndrome.[2]
One major contributor to post-hospital syndrome is medication related harm from drugs newly started or intensified during hospital admission.

In a linked article, Anderson and colleagues report a retrospective cohort analysis investigating the frequency of intensification of antihypertensive treatment at hospital discharge. The study reported that one in seven (14%) was discharged with intensified antihypertensive regimens. Of note, no difference was seen in rates of intensification between patients thought to be least likely to benefit from tight blood pressure control (those with limited life expectancy, dementia, or metastatic malignancy) and those thought to be most likely to benefit from tight blood pressure control (history of myocardial infarction or cerebrovascular disease).

The study did not determine whether intensified blood pressure control resulted in drug related harm. Data from other settings, including the landmark Systolic Blood Pressure Intervention Trial (SPRINT), show higher rates of adverse drug events with more aggressive blood pressure control, including hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure.[4 5] Elsewhere, starting antihypertensive treatment in older adults was associated with increased risk of hip fracture.[6]

Pressing concerns

Whether or not intensified antihypertensive treatment at hospital discharge results in measurable harm, the study findings highlight two pressing matters of concern to frontline clinicians and researchers: the need for a more judicious approach to the in-hospital management of chronic diseases, especially for older adults; and the need to move beyond more traditional means of medication reconciliation at hospital discharge.

The hospital inpatient setting is often a hazardous environment for older adults, where they are exposed to substantial physiological and psychological stress.[7] Inpatients are commonly sleep deprived and malnourished, feel pain and anxiety, and experience forced dependence and immobilisation.[2 8] These disturbances may provoke transient exacerbations of chronic diseases, including elevated blood pressure and blood glucose readings in inpatients with hypertension and type 2 diabetes mellitus, respectively. Reflex intensification of drug treatments used to manage these chronic diseases may result in overtreatment after discharge.[9 10]

Notably, in the study by Anderson and colleagues, predictors of intensified antihypertensive regimens included moderately and severely elevated inpatient blood pressure readings but not pre-admission outpatient blood pressure control.[3]

The inpatient setting may provoke transient exacerbations of chronic diseases, including elevated blood pressure

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Study answer and limitations One in seven older adults in this study (2074/14 915) were discharged with intensified antihypertensive regimens, more than half of whom (n=1082) had well controlled blood pressure before admission to hospital. This study relied on pharmacy and hospital records, so reasons for intensification of antihypertensives were not examined and drugs may have been intensified for indications other than hypertension.

What this study adds Elevated inpatient blood pressure recordings strongly predicted discharge with intensified antihypertensive treatment, even among patients with previously well controlled outpatient blood pressure and those with a low likelihood of benefit from strict blood pressure control. More attention is needed to reduce potentially harmful overtreatment of blood pressure as older adults transition from hospital to home.

Funding, competing interests, data sharing This study was supported by grants from the US National Institute of Aging. No additional data are available owing to a data use agreement with the US Department of Veterans Affairs.

The research also underscores the need for more comprehensive and robust medication reconciliation at hospital discharge

Clinicians should pursue a judicious approach to intensification of treatment that considers any reversible provoking causes (such as pain and anxiety), the risks and benefits of intensifying treatment (including the recognition that most risk associated with chronic diseases is incurred over the long term rather than the short term), and the availability of the clinician to reassess the effect of treatment throughout the remainder of the admission. Central to this process is the consideration of patients' preferences, including the option to intensify treatment in the outpatient rather than inpatient setting.

Anderson and colleagues' research also underscores the need for more comprehensive and robust medication reconciliation at hospital discharge. In the case of intensified antihypertensive treatment during hospital admission, the discharge reconciliation process should include measuring blood pressure before discharge to reassess the need for the intensification, communicating changes in antihypertensive treatment to all outpatient entities responsible for the patient, and ensuring prompt outpatient follow-up with the patient's primary care provider.

Overall, clinicians would be wise to adopt Sin City's famous tagline, "What happens in Vegas, stays in Vegas"; often the safest approach to inpatient chronic disease management is to let what happens in hospital stay in hospital.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.k3789

Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT)

Wen SW, White RR, Rybak N, et al on behalf of the FACT Collaborating Group

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Find this at: http://dx.doi.org/10.1136/bmj.k3478

Study question Can high dose folic acid supplementation (4.0 mg/day) from early (8-16 completed weeks of gestation) pregnancy until delivery be used as a prevention strategy for pre-eclampsia?

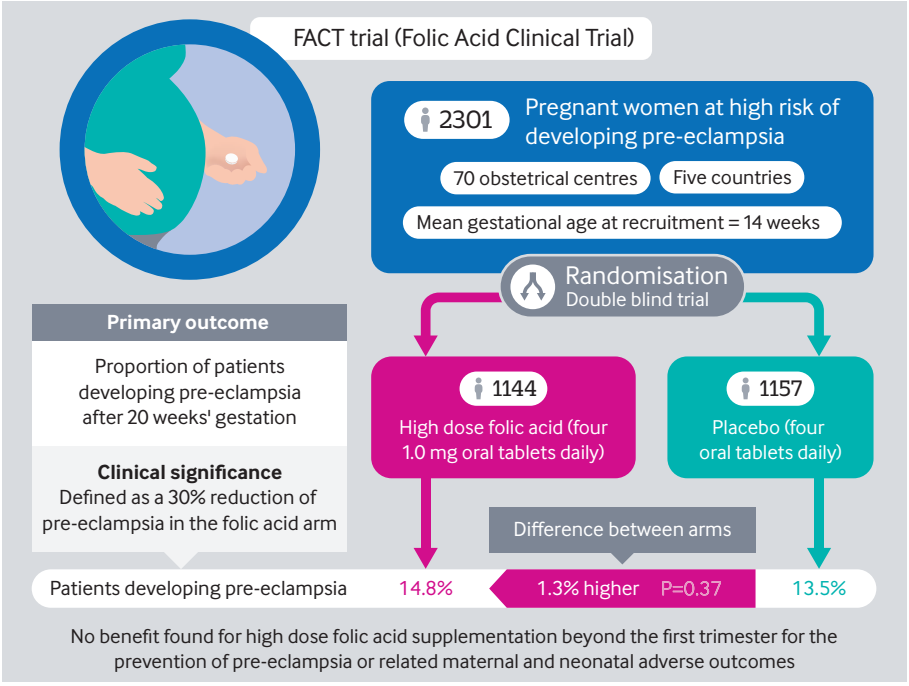
Methods The researchers carried out a randomised, phase III, double blinded international, multicentre clinical trial in 70 obstetric centres in five countries (Argentina, Australia, Canada, Jamaica, and the United Kingdom). 2464 pregnant women with at least one high risk factor for pre-eclampsia were randomised to high dose folic acid or placebo daily from eight to 16 completed weeks' gestation until delivery. The primary outcome was pre-eclampsia defined as hypertension presenting after 20 weeks' gestation with major proteinuria or HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome.

Study answer and limitations Pre-eclampsia occurred in 169/1144 (14.8%) women in the folic acid group and 156/1157 (13.5%) in the placebo group (relative risk 1.10, 95% confidence interval 0.90 to 1.34; P=0.37). No evidence of differences was found between the groups for any other adverse maternal or neonatal outcomes. Some international clinical practice guidelines changed the definition of pre-eclampsia during the trial.

What this study adds Supplementation with 4.0 mg/day folic acid beyond the first trimester does not prevent pre-eclampsia in women at high risk for this condition. However, supplementation remains indicated in preconception and early pregnancy for the prevention of neural tube defects, but there was a need to define when to discontinue supplementation, as current clinical practice guidelines do not provide clear guidance beyond the first trimester.

Funding, competing interests, data sharing This study was supported by grants (198801 and 98030) from the Canadian Institutes of Health Research. The authors have no competing interests. Data are available upon reasonable request.

Study registration Current Controlled Trials ISRCTN23781770 and ClinicalTrials.gov NCT01355159.



Comparison of maternal outcomes between study arms. Values are numbers (percentages) unless stated otherwise

Outcomes	Folic acid group	Placebo group	Relative risk (95% CI)	P value
Maternal death	0	0	Not applicable	Not applicable
Spontaneous abortion (miscarriage)	27 (2.3), n=1172	21 (1.8), n=1180	1.29 (0.74 to 2.28)	0.37
Placental abruption	12 (1.0), n=1169	19 (1.6), n=1179	0.64 (0.31 to 1.31)	0.21
Premature rupture of membranes	215 (18), n=1169	224 (19), n=1180	0.97 (0.82 to 1.15)	0.71
Gestational age <37 weeks	297 (26), n=1150	304 (26), n=1164	0.99 (0.86 to 1.13)	0.87
HELLP syndrome	6 (0.52), n=1144	5 (0.43), n=1156	1.21 (0.37 to 3.96)	0.75
Severe pre-eclampsia	24 (2.10), n=1144	16 (1.4), n=1156	1.52 (0.81 to 2.84)	0.19
Antenatal inpatient length of stay (days)	5.6 (7.7)*, n=221	5.2 (6.2)*, n=232	0.34 (7.0) (−0.96 to 1.63)†	0.61

HELLP=haemolysis, elevated liver enzymes, low platelets.
*Mean (SD).
†Mean (SD) difference (95% CI).