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Restoring the integrity of the clinical trial evidence base

A call to researchers and editors to help restore invisible and abandoned trials

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Public confidence in the credibility of medical research is at a low ebb.[1-4] Many completed clinical trials have never been published, and many published results are incomplete or misleading.[5-7] The resulting distortion of the evidence base is widely recognized and commonly decried.[8] It is one of the leading scientific problems of our time, but few solutions have been put forward.

In a linked Analysis article, Doshi and colleagues offer a bold remedy in the form of the RIAT (restoring invisible and abandoned trials) proposal.[9] Invisible trials are those that have never been published. Abandoned trials are unpublished trials that sponsors are no longer actively working to publish or published trials that, although documented as misreported, have not been corrected by the authors. Doshi and colleagues declare that, "because abandonment can lead to false conclusions about effectiveness and safety, we believe that it should be tackled through independent publication and republication of trials." They challenge medical researchers and funding agencies associated with unpublished or misreported trials to swiftly signal their intent to publish or correct these "abandoned" trials and then to act on this within a year. If no such intention is declared, or if a corrective paper has not been published within a year, they propose offering the opportunity to become "restorative authors" to other responsible researchers, who would restore the integrity of the reporting of the trials involved.

The RIAT proposal outlines the step by step process that the original authors or volunteer restorative authors should follow. It provides a minimum set of criteria for the proper and responsible publication and republication of abandoned studies. To help start this project, the proposers supply a list of internal company research reports in their possession; many were obtained from lawsuits or freedom of information policies. These documents provide detailed, previously confidential, information on a large number of clinical trials that are known to be unpublished or misreported. The authors of the proposal pledge to make these resources available to restorative authors and they call on others with similar holdings to do the same.

As the authors of this proposal explain, it is the existence of clinical study reports that makes it possible to reconstruct industry funded clinical trials. These reports are little known, highly structured internal company documents that describe the planning, execution, and results of individual clinical trials. Why not publish these reports instead of encouraging their distillation into short research reports for journals? These documents may be thousands of pages long and are not easily digestible: journal publication based on them may have a compression factor well above 1000:1.

The authors of the RIAT proposal are confident that the necessary trial information can be obtained from clinical study reports. They provide an audit record tool to ensure that essential information is sorted systematically and to minimize the effect of reporting biases. As well as committing to publication within a year, restorative authors must adhere to the study protocol and its prespecified objectives, as well as to other reporting standards. The aim is to make any value judgments and decisions clear.

If the evidence from past trials is unsound, so will be our view of new treatments

Nothing better underscores the urgency and importance of the RIAT proposal than the accompanying list of abandoned trials. Read it and weep: on the list are trials for drugs used by millions of people, including zanamivir, atorvastatin, gabapentin, and paroxetine. The number and variety of drugs show that incomplete reporting of clinical trial results is not an isolated occurrence. Rather, it is an entrenched and widespread problem. Secrecy and selective reporting were an integral part of the system. Reforms such as trial registration and mandatory results reporting will improve things in the future but can do nothing about the flawed evidence of the past.

The case in favor of the RIAT proposal is particularly compelling because new treatments are judged against those tested in past trials. If the evidence from past trials is unsound, so will be our view of new treatments. The failure to correct the scientific record is at odds with the principles of transparency that most in the wider medical community, including drug company leaders, now publicly espouse.[10] Despite the rhetoric, however, little has changed so far.

The RIAT proposal is the first to outline a clear practical means to an important end—an accurate understanding of the results of previously performed clinical trials. The proposal authors acknowledge that there are unresolved practical challenges and unforeseen consequences, and many of these challenges were highlighted during peer review of their paper. These problems mean that some will think the project is rash and overly ambitious, whereas others will inevitably think that it does not go far enough. In particular, because clinical study reports exist only for industry funded trials, non-industry funded trials that have been misreported or abandoned by their authors will not find an easy route into the RIAT fold.

We should not let these shortcomings prevent us from moving forward. Doshi and colleagues' unusual proposal is another step on the road towards a complete and unbiased account of the effectiveness and safety of medical interventions. We hope that the RIAT proposal will stimulate original researchers or capable volunteer restorative authors to come forward. As editors of the *BMJ* and *PLOS Medicine*, we endorse the proposal and commit to publishing restorative clinical trial submissions. We encourage other journals to signal their belief in the importance of this effort by endorsing the proposal too, either with an editorial in their journals or by responding to this editorial, encouraging submission of these publications.

The results of clinical trials are a public, not a private, good. The public interest requires that we have a complete view of previously conducted trials and a mechanism to correct the record for inaccurately or unreported trials. If we do not act on this opportunity to refurbish and restore abandoned trials, the medical research community will be failing its moral pact with research participants, patients, and the public. It is time to move from whether to how, and from words to action.

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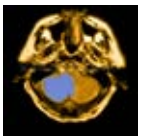

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Clinical features of stroke affecting the posterior circulation differ substantially from those of anterior circulation stroke

Posterior circulation stroke: still a Cinderella disease

Needs better recognition, specific diagnostic imaging, and studies of treatment

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Clinicians who treat patients with a transient ischaemic attack (TIA) or ischaemic stroke that affects the posterior circulation face difficulties in making the diagnosis, accessing imaging, and treating the condition effectively. Healthcare professionals in emergency settings urgently need to acquaint themselves with the signs of the acute neurological deficits associated with posterior circulation stroke.

Posterior circulation stroke accounts for about a fifth of the estimated 150 000 strokes that occur in the UK each year.[1] Simple screening methods have been devised to identify patients with an acute stroke or TIA and ensure early intervention. The "face arm speech test" (FAST) score in particular has been developed to assess whether a patient is likely to have had an acute stroke and may be a candidate for intravenous thrombolysis. This score was primarily evaluated in a cohort of unselected patients with acute stroke, most of whom had anterior circulation (carotid territory) stroke.

Clinical features of stroke affecting the posterior circulation (usually in the territory of the vertebrobasilar system) differ substantially from those of anterior circulation stroke. Common posterior circulation symptoms include visual disturbance, vertigo, and ataxia (box). The face arm speech test score does not include these features and is positive in only 61% of patients with posterior circulation stroke.[2]

Common clinical features of posterior circulation stroke

- Unilateral, bilateral, or crossed sensory loss or weakness
- Visual disturbance (such as diplopia and homonymous hemianopia)
- Unsteadiness or ataxia
- Dysarthria
- Dysphagia
- Vertigo
- Nausea and vomiting
- Drowsiness
- Various other features, including other cranial nerve deficits

Patients with anterior circulation stroke usually have clinical features that conform to a readily identifiable pattern. After successful initiatives to raise awareness, these patients are often swiftly connected with appropriate hyperacute stroke pathways on hospital arrival (or even after pre-hospital alert by a paramedic), although a need for further development and training in the community to improve pre-hospital recognition of stroke has recently been highlighted.[3]

However, it is difficult to recognise posterior circulation TIA and stroke, and considerable delays occur often. A recent cross sectional study of patients with acute stroke who were treated with intravenous thrombolysis found that the intervals to referral and treatment were significantly longer for posterior circulation strokes than for anterior circulation strokes.[4] A recent analysis of all potential ischaemic events during the 90 days preceding ischaemic stroke within a prospective population based incidence study highlighted an important problem: transient isolated brainstem symptoms that do not satisfy traditional definitions of TIA commonly precede definite vertebrobasilar stroke.[5]

The risk of early recurrent stroke is high in patients with vertebrobasilar stenosis.[6] However, there is rarely a second chance at diagnosis when the diagnosis of posterior circulation TIA or stroke is delayed or missed, and the result may be death or substantial disability, including devastating outcomes such as locked-in syndrome. It is therefore crucial that posterior circulation stroke is detected and diagnosed earlier.

Computed tomography of the brain has far lower sensitivity than magnetic resonance imaging in the diagnosis of posterior circulation ischaemia, especially when diffusion weighted magnetic resonance imaging is used.[7] Brain magnetic resonance imaging can be invaluable in confirming the location of a lesion, but it can be difficult to perform in unwell patients with acute stroke. It also has longer scan acquisition times than computed tomography, which can introduce delay in treatment.[8] Moreover, the appropriate selection of magnetic resonance imaging as the imaging modality of choice relies on the initial clinical suspicion of posterior circulation stroke, which is challenging, as already discussed.

Because computed tomography remains the first line brain imaging modality for acute stroke in the UK, it may be preferable to harness its full potential. In some cases, computed tomography angiography can rapidly identify the cause of a posterior circulation stroke lesion, including the location and severity of vascular disease. This technique may have greater sensitivity for vertebral artery dissection than magnetic resonance angiography or ultrasound, but further studies are needed.[9]

Treatment of posterior circulation cerebral ischaemia is also not straightforward. Initial medical management for posterior circulation TIA are the same as for anterior circulation TIA. Patients with posterior circulation ischaemic stroke are eligible for intravenous thrombolysis, but there are important areas of uncertainty. The role of endovascular therapy for posterior circulation acute ischaemic stroke is not clear. There are no clear selection criteria for acute neurosurgical intervention. It is also unclear exactly how patients with vertebral artery dissection or vertebral artery stenosis should be selected for secondary prevention interventions.

Of 656 participants in the recent Interventional Management of Stroke (IMS) trial III,[10] which compared intravenous thrombolysis with intra-arterial treatment against intravenous thrombolysis alone, the brainstem or cerebellum was the presumptive location of stroke in only 2% of patients. Patients with basilar artery occlusion will not be included in the UK's interventional stroke trial.[11]

Furthermore, patient selection, referral, and transfer for neurosurgical interventions such as external ventricular drainage for hydrocephalus due to mass effect from posterior circulation infarction can vary greatly.[12] In patients with confirmed vertebral artery dissection, it is unclear whether antiplatelet treatment or anticoagulation is the best treatment approach. This question is currently being investigated by the Cervical Artery Dissection in Stroke Study (CADISS).[13] For vertebral artery stenosis, it is not known whether vertebral artery stenting is superior to medical treatment, a question that the Vertebral Artery Ischaemia Stenting Trial (VIST) aims to answer.[14] A second trial is also investigating stenting for symptomatic vertebral artery stenosis.[15] Given the high risk of early recurrence of stroke in vertebrobasilar stenosis, urgent investigation and treatment are crucial.

Diagnosis and treatment trials have focused mainly on anterior circulation stroke. There is a clear need for studies that assess the optimal imaging protocols for posterior circulation stroke and treatment trials conducted solely in patients with posterior circulation stroke.

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Editorial: Responding to domestic violence in primary care (*BMJ* 2012;344:e757)
Clinical review: Violence between intimate partners: working with the whole family (*BMJ* 2008;337:a839)

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Intimate partner and sexual violence against women

A major public health problem that requires a compassionate and effective response

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Conditions, symptoms, and circumstances that may be associated with intimate partner violence[23]

- Symptoms of depression, anxiety, post-traumatic stress disorder, sleep disorders
- Suicidality or self harm
- Use of alcohol and other substances
- Unexplained chronic pain
- Unexplained chronic gastrointestinal symptoms
- Unexplained genitourinary symptoms, including frequent bladder or kidney infections
- Adverse reproductive outcomes, including multiple unintended pregnancies or terminations (or both), delayed pregnancy care, and adverse birth outcomes
- Unexplained reproductive symptoms including pelvic pain, sexual dysfunction, vaginal bleeding, and sexually transmitted infections
- Traumatic injury, particularly if repeated and with vague or implausible explanations
- Problems with the central nervous system, such as headaches, cognitive problems, hearing loss
- Repeated health consultations with no clear diagnosis
- Intrusive partner in consultations

On 20 June the World Health Organization published its first clinical and policy evidence based guidelines on responding to intimate partner violence and sexual violence against women.[1] These landmark guidelines draw from a WHO study of 24 097 women in 10 countries.[2] This study showed widespread lifetime physical and sexual violence by an intimate partner (15-71% prevalence among ever partnered women) and associated effects on health. The health effects of such violence are many (box).[3] The 2010 Global Burden of Disease Study ranked intimate partner violence fifth in terms of years lost owing to disability.[4]

The WHO guidelines offer 37 recommendations about the clinical care of women who have experienced intimate partner violence or sexual violence (or both), the training of healthcare providers, and the formulation of healthcare policy and service provision. They meet a crucial need to raise awareness of such violence as a health matter—rather than just a criminal justice, social, or personal problem—among healthcare providers, trainers, and policy makers.

A recent study of data from 70 countries (with varying religions, levels of income, and political systems), covering 85% of the world's population, found that the generation of public support and media attention through a strong autonomous feminist movement was the key catalyst for government action on violence against women.[7] This was more important than the wealth of a nation, the number of female politicians, or the positioning of parties on the left-right political spectrum. The current WHO guidelines may be used, alongside evidence based literature on the prevention of violence,[8] by civil society groups, health organisations, and others to push for national and local changes.

Best clinical guidance for women who have been sexually assaulted includes recommendations on the use of emergency contraception and post-exposure prophylaxis for HIV and sexually transmitted diseases, along with the offer of safe legal abortion and psychological interventions. In developed countries this knowledge can often be accessed through referral to specialised services, but in the developing world specialist sexual health services may be inaccessible to most women. There is a need for greater sexual health knowledge among primary healthcare workers.[9]

The WHO guidelines strongly recommend the use of targeted selective clinical inquiry to ask about intimate partner violence when women present in circumstances that may be associated with such violence, or with conditions that may be caused or complicated by it (box). A good example of a tool that can help with such inquiries was that used in the IRIS study conducted in English general practice, where medical records are computerised. An electronic prompt (HARK questions[10]) was used to encourage targeted inquiry and to lower the threshold for asking about abuse.[11] Universal screening for intimate partner violence, including screening masquerading as routine inquiry,[12-14] does not work. This conclusion is supported by a recent Cochrane review[15]; the Canadian Task Force on Preventive Health Care[16]; the UK Health Technology Assessment Programme[17]; and three large randomised controlled trials from the United States,[18] Canada,[19] and Australia.[20] The latest US Preventive Services Task Force recommendations support screening,[21] but when questioned after the recommendations were published, the task force acknowledged that there was no clear evidence to support the effectiveness of screening.[22]

The WHO guidance misses an opportunity to highlight that the competent clinical management of common conditions (such as depression or unexplained pain) should include inquiries about current or past intimate partner violence or sexual violence.[24] For health professionals and affected women, the recognition that abusive relationships can lead to health problems may serve as an impetus for change in clinical management or personal choices.[25]

WHO's recommendation that third sector specialist services be used to support a health service response to intimate partner violence is to be applauded. The report also recognises the importance of developing mental health services with expertise in post-traumatic stress disorder and child-adolescent mental health that take into account exposure to intimate partner violence and sexual violence. When advocacy services or referral options are lacking, a coordinated community response is required that involves local non-abusive men and emphasises the direct and indirect harm caused to men, children, and women from intimate partner violence and sexual violence (see http://tobisstory.moonfruit.com/). In the United Kingdom, funding for specialist support services for intimate partner violence—which stood at £97m (€115m; $149m) in 2008—has since been cut by a third. Yet the estimated total annual costs attributed to such violence are £16bn.[26] Globally, politicians give precedence to other concerns, such as the war on terror and on drugs. Yet many more women are harmed by intimate partners than by either of these, and it is time that the matter received equal attention.

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Many randomised trials have left us with a sobering realisation of the enormous challenges of changing doctors' behaviour

Interventions to enhance self management support

Add no noticeable value to the benefits of existing care for chronic conditions

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Effective interventions are often not feasible and feasible interventions are often not effective

Clinical trialists, interested in ensuring that their interventions are effective in the real world of clinical practice, have long called for study designs—termed practical, pragmatic, or effectiveness—that reflect practice as closely as possible.[1] These practical trials are particularly important in health services research, which can involve apparently effective interventions that are resource intensive and implemented by charismatic enthusiasts. Such interventions are likely to fail when introduced into settings with fewer resources by doctors preoccupied with the considerable stresses of everyday practice. In a linked paper by Kennedy and colleagues, we learn that effective interventions in health services are often not feasible and—as revealed by practical trials—feasible interventions are often not effective.[2]

In a cluster randomised controlled trial, Kennedy and colleagues investigated whether self management interventions targeting care providers could improve outcomes over 12 months in patients with diabetes, chronic obstructive pulmonary diseases, and irritable bowel syndrome. The investigators went to great lengths to implement a practical trial design. Their intervention was brief, consisting of only two sessions with staff from primary care clinics. Attendance at the two training sessions was high (90% and 82%, respectively), and most attendees rated the sessions at least moderately positively (mean score >2.5 on a five point scale). However, 42% of physicians reported no use of a tool to assess patient support needs and priorities, which was at the heart of the intervention. Patient reports confirmed failure of implementation. Inevitably, the intervention had no effect on health related quality of life, self efficacy, resource use, or many secondary outcomes.

Does this report represent an isolated failure of interventions for self management support directed as care providers? Unfortunately, it does not. Previous randomised trials have focused largely on educational and telehealth interventions directed at patients, with the ultimate goal of enhancing health outcomes and reducing costs.[3-5] Many such trials have investigated various interventions for self management of patients with diabetes, asthma, heart failure, irritable bowel disease, depression and pain. Some studies suggested benefits on outcomes such as quality of life, symptoms (for example, pain), social function, and psychological wellbeing,[3-8] although others did not.

The few studies testing interventions of self management support that focus on care providers provide even less encouragement. Their results, in keeping with the current study, have been completely negative. Among these trials,[9-11] not only did the outcomes of interest not differ between intervention and control groups, but investigators were—again, as in the current study—unable to document significant differences in the implementation of self management support.

Had doctors implemented the self management supports as planned, would these trials have resulted in important benefits for patients? Although the results of patient level trials suggest that they might, the failure to implement leaves considerable doubt. Implementation is not an all or nothing phenomenon (although what has happened thus far seems quite close to nothing), and the degree of implementation that might realistically be achieved through more intensive interventions remains uncertain. Furthermore, whether doctors have the skills and training to do a good job is also uncertain.[5]

The difficulties in implementing self management support in pragmatic clinical trials is best understood in the context of the broader literature on changing doctors' behaviour [12] Many randomised trials have left us with a sobering realisation of the enormous challenges of such behavioural change. One important contextual problem is the competing demands on the care of long term conditions that doctors face in the trial. Another is the understanding and motivation of the healthcare team. In the current trial, one might seriously question doctors' awareness of the importance of patient self management of chronic conditions. After all, they not only refused to participate in additional training beyond the first two sessions, but also refused to allow monitoring of the fidelity of the intervention.

It is evident that the failure of care directed interventions to enhance patient self management results from inadequate consideration of the relevant attitudes and possibly skills of doctors and the obstacles of time, inertia, and competing priorities. Considerable incentives will probably be needed to change doctors' behaviours with respect to self management support practices. The authors' ultimate conclusion is even more pessimistic: "perhaps we should abandon current models of both provider and patient based self management support for innovative interventions." Although they may be right, experience with current models mandates careful study of all possible obstacles, and even then a high level of skepticism regarding all future efforts in this area.

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