

Antipyretic treatment for feverish young children in primary care

No persuasive evidence for combining paracetamol and ibuprofen



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Fever is one of the main concerns that parents have when their child is unwell. Many parents believe fever is potentially harmful and worry about its height and duration. It is standard practice for health professionals to give advice about administering antipyretic drugs to children. The most commonly used drugs are paracetamol (acetaminophen) and ibuprofen. Because these drugs can be given at alternating intervals some doctors tell parents to use a combination of both drugs during the course of a febrile illness.

In the linked study ([doi:10.1136/bmj.a1302](https://doi.org/10.1136/bmj.a1302)), Hay and colleagues report a randomised controlled trial of paracetamol, ibuprofen, and a combination of the two drugs in 156 febrile children age 6 months to 6 years in primary care. The trial has two primary outcomes—time without fever in the first four hours and fever associated discomfort after 48 hours.¹ Hollinghurst and colleagues compare the costs to parents and the NHS of the three drug regimes.²

The scale of childhood fever and treatment costs is large. In the Avon longitudinal study of parents and children, parents reported fever as a symptom in more than two thirds of children under 5 years, and a third of these children had been taken to a doctor for a consultation.³ The large volume of calls and consultations for childhood fever has a substantial effect on NHS direct, out of hours services, and accident and emergency care services. In 2004 the expenditure in Europe on over the counter paracetamol and ibuprofen for children was £405m (€511m; \$756m).²

Yet a National Institute for Health and Clinical Excellence review of feverish illness in children found no evidence that reducing temperature shortens the duration of illness or reduces complications, such as febrile convulsions.⁴ In fact, reducing fever may prolong illness. In a trial of paracetamol in 50 children with *Plasmodium falciparum*, the clearance time of the malaria parasite was 16 hours longer in children treated with quinine and paracetamol than in those treated solely with quinine.⁵ Similarly, in a trial of paracetamol in 72 children with chickenpox, the time to total scabbing was significantly longer in the paracetamol group.⁶

Paracetamol and ibuprofen are effective at reducing temperature and ibuprofen acts for longer than paracetamol.⁷ The largest trial comparing paracetamol, ibuprofen, and an alternating combination was conducted in paediatric community centres in Israel.⁸ In total, 464 febrile children age 6–36 months were randomly allo-

cated into three groups. The group that received an alternating combination had a significantly lower mean fever over three days, a decline in a validated checklist of children's pain, and fewer drug doses. However, the study is difficult to interpret because the investigators used a complicated design, which loaded each of the three groups of children with either paracetamol or ibuprofen at study entry.

When advising parents to use antipyretics, professionals are trying to reduce the child's discomfort associated with fever and manage the parents' anxiety. Time without fever is arguably a proxy of parental concern, so the most important primary outcome examined in the trial by Hay and colleagues is discomfort associated with fever at 48 hours. Recruiting large numbers of children with acute illness in primary care into research studies is difficult, and Hay and colleagues were unable to recruit enough children to give sufficient power to detect differences for this outcome. But their data suggest no additional improvement in fever associated discomfort or activity levels in the combined drug group at 24 hours, 48 hours, and five days. A trial with greater power would be needed to confirm this.

Hollinghurst and colleagues' economic analysis confirms that the cost associated with childhood fever is predominantly borne by parents and primary care. The authors constructed a cost consequences matrix of results at 48 hours and five days using costs to the NHS and parents, and they combined discomfort, activity, appetite, sleep, and resolution of fever to determine a variable "returned to normal for that child." Their data show no significant differences between the drug regimens.

Paracetamol and ibuprofen are safe for children when given at the recommended doses. Despite a commonly held view, no evidence exists that ibuprofen exacerbates wheeze in children.⁹ However, in the United Kingdom ibuprofen is not licensed for children under 3 months or for those who weigh less than 5 kg. The most worrying aspect of the study by Hay and colleagues is that even under clinical trial conditions, 31 children received a drug overdose. This suggests that parents may often inadvertently exceed the maximum recommended dose and that a more complicated alternating regimen of paracetamol and ibuprofen may be less safe than using either drug alone.

No persuasive evidence exists for recommending a combination or an alternating regimen of paracetamol and ibuprofen. Doctors should try to improve their

precision of diagnosis in febrile children, and parents should be reassured that fever itself is not harmful. The importance of fluid intake and sensible clothing should be discussed. Before prescribing it may be important to weigh the child to determine the most appropriate dose of antipyretic. The longer action of ibuprofen makes it the most suitable antipyretic to use.

- 1 Hay AD, Costelloe C, Redmond NM, Montgomery AA, Fletcher M, Hollinghurst S, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. *BMJ* 2008;337:a1302.
- 2 Hollinghurst S, Redmond N, Costelloe C, Montgomery A, Fletcher M, Peters TJ, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): economic evaluation of the randomised controlled trial. *BMJ* 2008;337:a1490 (in press).
- 3 Hay AD, Heron J, Ness A, ALSPAC Study Team. The prevalence of symptoms and consultations in pre-school children in the Avon

longitudinal study of parents and children (ALSPAC): a prospective cohort study. *Fam Pract* 2005;22:367-74.

- 4 National Institute for Health and Clinical Excellence. *Feverish illness in young children: assessment and initial management in children younger than 5 years*. 2007. www.nice.org.uk/nicemedia/pdf/CG47NICEGuideline.pdf.
- 5 Brandts CH, Ndjavé M, Graninger W, Kremsner PG. Effect of paracetamol on parasite clearance time in *Plasmodium falciparum* malaria. *Lancet* 1997;350:704-9.
- 6 Doran TF, De Angelis C, Baumgardner RA, Mellits ED. Acetaminophen: more harm than good for chickenpox? *J Pediatr* 1989;114:1045-8.
- 7 Wahba H. The antipyretic effect of ibuprofen and acetaminophen in children. *Pharmacotherapy* 2004;24:280-4.
- 8 Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. *Arch Pediatr Adolesc Med* 2006;160:197-202.
- 9 Kanabar D, Dale S, Rawat M. A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma-related symptoms. *Clin Ther* 2007;29:2716-23.

Medical law and protection of children

Better guidance is needed on how doctors working in child protection should manage their conflicting professional duties

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A crisis of confidence is developing between the General Medical Council (GMC) and paediatricians. Some assert that the GMC does not adequately understand the unique nature of child protection work,¹ which the GMC refutes.² We argue that this reflects a fundamental confusion in doctors' duties regarding child protection, the consequences of which are exacerbated by the GMC's fitness to practise procedures.

Child protection guidance in the United Kingdom is underpinned by the 1989 Children Act. It introduced the "principle of paramountcy" of the child's welfare over all other competing considerations, to which UK child protection and paediatric guidance now refers. However, this principle only applies to the courts' criteria for deciding the outcome of cases under that act,³ not to doctors, whose medical and legal duties in child protection are governed by the usual body of medical law.

Medical law states that a doctor's duty to the (non-competent) child is owed to the parent, whose consent is required for the doctor to treat.⁴ This is supported by article 8 of the European Convention on Human Rights, as a consequence of both children's and parents' rights to family and private life. Thus, doctors have a duty of care to both, as recognised by the guidance of the GMC and Royal College of Paediatrics and Child Health. In child protection cases, these duties are likely to conflict. But although such differences should be resolved in the child's favour, little guidance is available on how the duty of care to the parent should be compromised beyond maintaining an aspiration to "partnership" with the suspected carer in caring for the child.⁵ This fits ill with practice,⁶ and may also conflict with the subsequent duty to the court should the doctor be required to act as an expert witness later.⁷

Thus, in many if not all child protection investigations there will be *prima facie* evidence that the doctor acted contrary to the usual duty of care expected towards the child's parents, as fluctuating suspicion pushes the pae-

diatrician uncertainly from role to role. Because child protection should be preventive, in many cases no abuse will be detected retrospectively to justify this breach of care.

Although the GMC's latest guidance is silent on this,⁸ it states publicly that it appreciates such dilemmas and asserts that few doctors working in child protection have been subject to fitness to practise procedures. However, should a case become "high profile"—either because of media coverage or the reputation of the doctor—additional concerns arise.

In fitness to practise proceedings, the current term, "misconduct," subsumes the old term, "infamous conduct in a professional respect"—behaviour by a doctor that brings the profession into disrepute.^{4,9} Thus, a skilful and hostile media campaign is a salient additional factor that the GMC must consider in its deliberations. If the doctor claims to be specially skilled, the standard set needs to be based on reasonable practice of that level of skill, which may be judged by a court independent of customary practice by colleagues.¹⁰

The purpose of any GMC sanction is not only to protect the public but to maintain public confidence in the profession—something that again must be considered in the light of media coverage. These pressures converge to make it less likely for the GMC to dismiss cases related to a media campaign and, especially if the doctor is claiming special skills, to assess the case more stringently. It is easy to see how an ordinary child protection doctor could interpret the GMC's response to high profile cases as "appeasing the media" and become concerned by criticisms of lapses in care to the parent, which the doctor understands as unavoidable consequences of ordinary child protection practice. The GMC can equally claim that it is correctly following its procedures to protect both the public and the reputation of medicine.

The number of complaints against paediatricians related to child abuse work increased by more than 500% in

between 1995 and 2003, with 61% of currently active complaints being made after 2003.¹¹ Since 2003, registrations for emotional abuse and neglect have increased, but those for physical or sexual abuse have declined.¹² This suggests that paediatricians may be avoiding work related to abuse, for which more detailed physical examinations are needed. If so, this is bad for children.

Three interventions are urgently needed. Firstly, the GMC should collaborate with other professional bodies to issue more specific guidance about how doctors should manage these conflicting duties of care in child protection cases. Such guidance—to which doctors could work, and against which they could be judged—would do much to restore confidence in child protection processes. Secondly, complaints about professionals in child protection cases should be subject to independent scrutiny before they are referred to their professional bodies. This process could separate matters of poor professional practice from those of public confidence, but at present no body exists that can do this. Finally, the general public needs to be better informed about the reality of everyday

child protection work, so that the necessary compromises implicit in such procedures are better understood.

- 1 Williams C. United Kingdom General Medical Council fails child protection. *Pediatrics* 2007;119:800.
- 2 Hawkes N. GMC denies "hounding" paediatricians. *Times Online* 2007 June 26. www.timesonline.co.uk/tol/life_and_style/health/article1985653.ece.
- 3 Brayne H, Martin G, Carr H. *Law for social workers*. Oxford: Oxford University Press, 2001.
- 4 Kennedy I, Grubb A. *Medical law*. London: Butterworths, 2000.
- 5 HM Government. *Working together to safeguard children*. London: Stationery Office, 2006.
- 6 Bell M. Working in partnership in child protection: the conflicts. *Br J Social Work* 2003;29:437-55.
- 7 General Medical Council. *Acting as an expert witness*. London: GMC, 2008.
- 8 General Medical Council. *0-18 years: guidance for all doctors*, 2007. www.gmc-uk.org/guidance/archive/GMC_0-18.pdf.
- 9 General Medical Council. *Medical Act 1983*. 2007. www.gmc-uk.org/about/legislation/medical_act.asp.
- 10 General Medical Council. *Indicative sanctions guidance for fitness to practise panels*. London: GMC, 2005.
- 11 Turton J, Haines L. *An investigation into the nature and impact of complaints made against paediatricians involved in child protection procedures*. London: Royal College of Paediatrics and Child Health, 2007.
- 12 Department for Children, Schools and Families. *Referrals, assessments and children and young people who are the subject of a child protection plan or are on child protection registers, England—year ending 31 March 2007*. London: DCSF, 2007.

Community treatment orders

Insufficient evidence exists to support the new legislation for England and Wales



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Community treatment involves the use of mental health legislation to impose varying requirements on some mental health patients who live in the community. The Mental Health Act 1983 made no comprehensive provision for community treatment. This has meant that some patients who improve in hospital are discharged to the community, become non-compliant with medication, and have a relapse. The Mental Health Act 2007, which will come into force in England and Wales in November 2008, sets out how supervised community treatment should work.

The new legislation applies only to patients detained in hospital for treatment. The clinician responsible for the patients' care may discharge them from hospital under a supervised community treatment order. The order can specify variable conditions that the patient must abide by, including the need to comply with medication. The order is renewable and can be discharged only by the responsible clinician or a mental health review tribunal. The patient can be recalled to hospital if they deteriorate or fail to keep to certain conditions. If medication is to be given forcibly this must occur within hospital.

The concept of compulsory community treatment is not new. It was first formally raised when the Mental Health Act 1959 was under review.¹ In 1987, the Royal College of Psychiatrists published *Community Treatment Orders: A Discussion Document*, but it did not raise much support.² In 1994, the college held a debate regarding the matter, and the final vote went three to two against the introduction of such orders.³ In February 2000, a similar debate was held at the Maudsley Hospital, London.⁴ The advantage of this debate was that it was

open to the public and included patients and carers. Arguments supporting their introduction were based on the belief that it is best to treat people with severe mental illness in the least restrictive environment. The final vote was 57% against and 34% in favour.

Theoretically, community treatment orders could help improve public protection by ensuring that patients comply with their medication, but this idea is not greatly supported by evidence. A study in the United Kingdom in 2005 collected data for homicides in England and Wales between April 1999 and December 2003.⁵ It found that of the 2670 homicide convictions, 249 people who committed homicide had contact with mental health services in the year before the offence, which suggests that around 50 homicides a year are committed by psychiatric patients in the community. The study found that 40 of the 249 homicides—about eight each year—were committed by previously detained patients after non-compliance with medication or loss of contact with services. Although these deaths could arguably have been avoided, 557 homicides were committed by patients with a lifetime history of mental disorder who had not been in contact with mental health services in the year before the offence. This suggests that twice as many homicides are committed by patients with mental health problems who have not been in recent contact with mental health services. Risk assessment conducted during the final contact with the 249 cases seen in the year prior to the offence, found that immediate risk of violence was judged to be either not present or low in 220 cases. Thus the relative effect of community treatment orders on homicides is likely to be minimal.

A UK report in 2005 suggested that over the next 10-15 years the number of people with community treatment orders in England and Wales may rise to between 7800 and 13 000.⁶ However, this increase would be countered by fewer people being detained as inpatients. The predicted costs of implementing supervised community treatment in England and Wales will be £3.4m (€4.3m; \$6.7m) in the first year, increasing to £21.2m in 2014-5.⁷ This should be considered against savings related to a reduction in the use of hospital beds, which could be £8.7m in the first year and increase to £47.7m by 2014-5.⁷

A large independent review of community treatment orders, which included 72 international studies conducted over the past 30 years, found little evidence of a positive effect on outcomes, such as hospital readmission rates, length of stay, or compliance with drugs. Furthermore, these orders cannot work without adequate resources or the general support of providers of mental health care.⁸ A Cochrane review, which included two randomised trials, concluded that community treatment orders may not be an effective alternative to standard care.⁹

The provision of community treatment orders within the Mental Health Act 2007 may benefit some patients;

however, these orders have been introduced without evidence to support them. It remains to be seen how clinicians will make use of the legislation and whether it provides patients, carers, and their families with positive experiences.

- 1 Department of Health and Social Security. *A review of the mental health act 1959*. London: Stationery Office, 1976.
- 2 Royal College of Psychiatrists. *Community treatment orders: a discussion document*. London: Royal College of Psychiatrists, 1987.
- 3 Turner T. Compulsory treatment in the community: some debating issues. *Psychiatr Bull* 1994;18:657-65.
- 4 Pinfold V, Bindman J. Is compulsory community treatment ever justified? *Psychiatr Bull* 2001;25:268-70.
- 5 University of Manchester. *Avoidable deaths: five year report of the national confidential inquiry into suicide and homicide by people with a mental illness*. 2006. www.medicine.manchester.ac.uk/suicideprevention/nci/Useful/avoidable_deaths_full_report.pdf.
- 6 Lawton-Smith S. *A question of numbers: the potential impact of community-based treatment orders in England and Wales*. London: King's Fund, 2005. www.kingsfund.org.uk/publications/kings_fund_publications/a_question_of_1.html.
- 7 Department of Health. *Mental health bill 2006: regulatory impact assessment*. London: Stationery Office, 2006. www.dh.gov.uk/en/Publicationsandstatistics/Legislation/Regulatoryimpactassessment/DH_062689.
- 8 Churchill R. *International experiences of using community treatment orders*. Institute of Psychiatry, 2007. www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_072730.
- 9 Kisely S, Campbell L, Preston N. Compulsory community and involuntary outpatient treatment for patients with severe mental disorders. *Cochrane Database Syst Rev* 2005;(3):CD004101.

Evidence based medicine and the medical curriculum

The search engine is now as essential as the stethoscope



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What we know about diseases, diagnosis, and effective treatments is growing rapidly. Today health professionals cannot solely rely on what they were first taught if they want to do the best for their patients. It has repeatedly been shown that clinical performance deteriorates over time.¹ A commitment to lifelong learning must be integral to ethical professional practice. However, the speed of the increase in knowledge—more than 2000 new research papers are added to Medline each day—represents a challenge.² The skills needed to find potentially relevant studies quickly and reliably, to separate the wheat from the chaff, and to apply sound research findings to patient care have today become as essential as skills with a stethoscope.

The advent of “evidence based medicine” saw an explosion of systematic reviews and guidelines but much less change in the medical curriculum.^{3 4} Although evidence based guidelines may help clinicians in selected areas, they cannot cover the range of questions or have the timeliness that clinical practice needs. Individual practitioners therefore need to be able to find and use evidence themselves—a 21st century clinician who cannot critically read a study is as unprepared as one who cannot take a blood pressure or examine the cardiovascular system. The medical curriculum should reflect this importance of changing information for today’s practitioner—the necessary skills must be taught and assessed with the same rigour as the physical examination.

How and when should these skills be taught? Just as we teach undergraduate students the basics of cardiac

anatomy and using a stethoscope, we should also teach them the anatomy of research and the basic knowledge and skills for evidence based practice (as set out in the Sicily statement⁵). These basic skills of using (not doing) research—searching, appraising, and applying research evidence to individual patients—should be taught early and applied as an integral part of learning in all years of the curriculum. But to be integrated with clinical skills they must also be regularly applied in the clinical setting.⁶ Graduation should be conditional on students showing that they have the skills to do this; for example, by producing a portfolio of critically appraised topics. The pedagogic approaches used should foster a commitment to lifelong learning.⁶

Postgraduate training and practice should build on this grounding through repeated application in everyday clinical work and the development of more advanced knowledge and skills. Doctors—whether at foundation level or in specialist training—should regularly log and discuss clinical questions, produce critically appraised topics, lead evidence based “journal clubs,” and participate in the audit of practice change.⁷ Such training has been shown to increase appropriate treatment.⁸ However this evidence is from a before-after study not a randomised trial, and further development of, and research on, workplace learning is urgently needed if we are to make best use of the billions of pounds spent annually in medical research.

Several elements are needed to achieve these changes. Firstly, both undergraduate and postgraduate healthcare

courses should explicitly require the development and demonstration of these skills. Embedding the evaluation of these skills into professional examinations and competencies will encourage their uptake and ensure that they have been learnt appropriately. Secondly, we need sufficient numbers of teachers and role models. This requires training and developing a cadre of leaders in clinical epidemiology; this should include people who are already senior to act as role models and those who are training to provide leadership in the future. Ring fenced funding should be provided to support people in training and course development. Thirdly, a catch-up programme of training in evidence based skills should be provided for those who qualified without the opportunity to develop these skills, through, say, a series of short workshops or courses in evidence based practice. Finally, we need further development of the infrastructure, in addition to systems to support evidence based practice and to increase awareness of its importance in managers and others as a way to facilitate responsive change (a prerequisite for responding to evidence).

The proposals above are timely given the changes to postgraduate training⁹, the investment in information technology infrastructure¹⁰, and the Department of Health's massive investment in the National Library for Health, processes to produce evidenced based national guidance (such as the National Institute for Health and Clinical Excellence), and ways of synthesising evidence (such as the National Coordinating Centre for Health Technology Assessment and the Cochrane Collaboration). The investment has been

truly enormous—literally billions of pounds. We believe that a relatively small expenditure on developing the skills of the users of these resources will help translate the resultant evidence based guidance, research findings, and knowledge into changes in practice, thereby improving the quality of health care.

If today's practitioners are to retain their professionalism, clinicians' information and research appraisal skills need to be improved urgently. Otherwise they risk being rapidly overtaken by administrators and patients who may not be able to use a stethoscope but are comfortable using Google, Wikipedia, and the internet.

- 1 Choudhry NK, Fletcher RH, Soumerai SB. Systematic review: the relationship between clinical experience and quality of health care. *Ann Intern Med* 2005;142:260-73.
- 2 Eady A, Glasziou P, Haynes B. Less is more: where do the abstracts in the EBM journal come from? *Evid Based Med* 2008;13:3.
- 3 EBM Working Group. Evidence based medicine: a new approach to teaching the practice of medicine. *JAMA* 1992;268:2420-5.
- 4 Sackett DL, Rosenberg WM, Gray JAM, Haynes RB, Richardson WS. Evidence-based medicine: what it is and what it isn't. *BMJ* 1995;312:71-2.
- 5 Dawes M, Summerskill W, Glasziou P, Cartabellotta A, Martin J, Hopayian K, et al. Sicily statement on evidence-based practice. *BMJ Med Educ* 2005;5:1.
- 6 Coomarasamy A, Khan KS. What's the evidence that postgraduate teaching in evidence based medicine changes anything? A systematic review. *BMJ* 2004;329:1017-9.
- 7 Straus S, Richardson S, Glasziou P, Haynes RB. *Evidence-based medicine: how to practice and teach EBM*. 3rd ed. Edinburgh: Churchill-Livingstone, 2005.
- 8 Straus SE, Ball C, Balcombe N, Sheldon J, McAlister FA. Teaching evidence-based medicine skills can change practice in a community hospital. *J Gen Intern Med* 2005;20:340-3.
- 9 Tooke J. Aspiring to excellence: final report of the independent inquiry into Modernising Medical Careers, 2008. www.mmcinquiry.org.uk/draft.htm
- 10 Cross M. Will Connecting for Health deliver its promises? *BMJ* 2006;332:599-601.

Translational research

From evidence based medicine to sustainable solutions for public health problems

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Enormous efforts have been made to establish evidence based medicine, to protect patients from ineffective or harmful treatments and unjustified claims while ensuring that appropriate treatments are offered. A simplistic view presupposes that after treatments are rigorously evaluated, results are incorporated into clinical guidelines within best practice criteria, which, in turn, inform policies. However, the process that leads to effective sustainable solutions to health problems is in fact non-linear, with different forms of evidence needed at different stages by different parties.

Even the concept of scientific evidence is fairly new. Randomised controlled trials only came to the fore after the discovery of antibiotics in the 1940s.¹ For some people, the rightful dominance of such trials in evidence hierarchies² has meant that they form the only acceptable evidence of treatment efficacy and safety in health research. Although it is agreed that treatments based on anecdotal evidence should be rejected, some vital evidence from non-randomised controlled trials has previously been devalued or dismissed. Such research suffers from lack of funding and a lower priority for publication.^{3 4}

Diseases such as cancer, diabetes, and heart disease

are seldom cured but may be modified, even prevented, by improving diet and lifestyle. Controlled experimental approaches are sometimes possible but are slow and expensive, and they are often not best suited to testing multiple interventions alongside complex lifestyle changes over long time periods. Well conducted cohort studies, non-randomised clinical trials, and preintervention or postintervention prevalence studies are now beginning to be accepted as providing strong enough evidence to justify recommendations for action.⁴⁻⁷

The research process that explores needs, develops potential treatments in basic laboratory research, and tests safety and efficacy in randomised clinical trials—"bench to bedside"—is phase 1 translational research.^{8 9} However, although treatments may prove safe and efficacious for selected volunteers in randomised clinical trials, further research is always necessary on treatment needs in routine practice settings, and this is another form of translational research.^{9 10} Signs, symptoms, causes of disease, and the outcome if left untreated all influence the need and type of treatment. Demographic factors modify patients' needs, clinical decisions, and treatment responses, highlighting the need for careful observational

research. Patients and doctors have differing priorities, as do the agencies that ultimately fund interventions. To ensure optimal management of disease in diverse populations and to guide strategy or health policy qualitative and situational factors need to be assessed more comprehensively.

Phase 2 translational research examines how findings from clinical science function when they are applied routinely in practice, amidst varying secular pressures.³ It informs guidelines about acceptability, effectiveness, and cost efficiency in ecological settings and policies to promote uptake and optimal use. For example, consumer research explores patients' behavioural responses to interventions and provides important insights into compliance; health economics adds the evaluation of cost effectiveness and cost avoidance. These needs challenge hierarchical views of "research quality" and funding allocation, traditionally dominated by randomised controlled trials, and point to the need for non-hierarchical typological approaches.⁵ Valuable parallels exist from successful commercial and product developments, which use multidisciplinary non-experimental research to inform incremental improvements,⁴ within some form of continuous improvement methodology—"kaizen" to its Japanese pioneers. Governments are increasingly demanding the integration of these new and developing research fields through agencies such as the United Kingdom's National Institute for Health and Clinical Excellence.

Ultimately, governments want enduring evidence based policies.¹¹ Phase 3 translational research (figure) also incorporates research processes to evaluate the complex interacting environmental and policy measures that affect susceptibility to disease and sustainability of clinical and public health management strategies. Controlling obesity and related lifestyle diseases will require an integrated view of education; environmental modifications to facilitate greater physical activity; and fiscal and regulatory changes to promote production, promotion, and delivery of healthier meals and total food supply. Practitioners, policy makers, and the public need sound evidence from different and new methods, involving both experimental and non-exper-

imental methodologies,^{4,5} that are sensitive to cultural and ethnic priorities. The ongoing evaluation of New Zealand's 10 year Healthy Eating Healthy Activity programme—which involves qualitative assessments of processes and policy implementation, integrated with quantitative evaluations of behavioural outcomes, and incorporating experimental assessments of specific strategy components—is such an example.¹²

Policy changes to reduce non-communicable diseases are complex and challenging. Reliance on actions within health services will be insufficient to control relentless rises in obesity, diabetes, and associated diseases. We need more effective treatments, but we must stop regarding clinical science and the ecological support from effective policies as independent disciplines, and we must adjust biases in funding and publication to reflect a more integrated view of what research is necessary.

Like the randomised controlled trial, translational research originates from the endeavours of the drug industry, but its full scope is far more wide reaching. It provides sustainable solutions for health problems and progresses beyond evidence based medicine into translational medicine, and perhaps into translational health strategy. Doctors must already make evidence based treatment decisions and monitor their outcomes. Politicians and policy makers also need to access best quality evidence and show how it informs the development of policies. Training in translational research methods (table, see bmj.com) for clinicians, guideline writers, grant awarding bodies, and policy makers would enable better assessment of complex evidence bases, help to integrate effective and culturally sensitive interventions with supporting environmental changes, and encourage continuous improvement of evidence based public policies. It would be in the interest of all parties for such training programmes in translational research to be established.

- 1 Doll R. Controlled trials: the 1948 watershed. *BMJ* 1998;317:1217-20.
- 2 Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323:334-6.
- 3 Hiss RG. Fundamental issues in translational research. Translational research—two phases of a continuum. In: *From clinical trials to community: the science of translating diabetes and obesity research*. Natcher Conference Center, National Institutes of Health, Bethesda, Maryland, USA, 2004:11-4. www.niddk.nih.gov/fund/other/Diabetes-Translation/conf-publication.pdf.
- 4 Berwick DM. Broadening the view of evidence-based medicine. *Int J Qual Saf Health Care* 2005;14:315-6.
- 5 Petticrew M, Roberts H. Evidence, hierarchies, and typologies: horses for courses. *J Epidemiol Commun Health* 2003;57:527-9.
- 6 World Cancer Research Fund. *Food, nutrition, physical activity and the prevention of cancer: a global perspective*. 2007. www.dietandcancerreport.org/.
- 7 Des Jarlais DC, Lyles C, Crepaz N, the TREND Group. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. *Am J Public Health* 2004;94:361-6.
- 8 Narayan VKM, Benjamin E, Gregg EW, Norris SL, Engelgau MM. Diabetes translation research: where are we and where do we want to be? *Ann Intern Med* 2004;140:958-63.
- 9 Hiss RG. The concept of diabetes translation: addressing barriers to widespread adoption of new science into clinical care. *Diabetes Care* 2001;24:1293-6.
- 10 Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet* 2005;365:82-93.
- 11 Cabinet Office. *Modernising government*. London: Stationery Office, 1999.
- 12 New Zealand Ministry of Health. Healthy Eating Healthy Action Newsletter. Issue 5, 2007. [www.moh.govt.nz/moh.nsf/pagesmh/5663/\\$File/heha-newsletter-sept07.pdf](http://www.moh.govt.nz/moh.nsf/pagesmh/5663/$File/heha-newsletter-sept07.pdf).

A 21st century view of translational research to provide sustainable solutions for health problems. This model, portrayed as linear, is inevitably oversimplistic. Each step can generate new research questions, which must be answered through a research continuum that requires different methods and constant two way engagement with the global research community. Research managers need to understand the whole process and the range of methods used

