Letters

One-time general consent for research on biological samples

Opt out system for patients is optimal and endorsed in many countries

Editor—Wendler's valuable overview of empirical studies of patients' preferences about the use of residual (leftover) tissue for research is not complete.[1] The discussion has already been settled by legislation in many countries.

In 2004 the Danish act on patient rights was amended with an opt out system for using residual tissue for research. In 2004 the US Office for Human Research Protections (OHRP) issued guidance that research on residual tissue which is anonymous to the researcher is not human subject research and therefore the tissue can be used without consent.[2] Earlier the Dutch Federation of Medical Research Societies' code of conduct on research with residual tissue drafted with patients' organisations had an opt out system for research on samples anonymous to the researcher.[3] In the recent UK Human Tissue Act no form of consent is needed for the use of fully anonymous or coded (or linked) residual tissue that is anonymous to the researcher, provided that an ethical review board has permitted the study. The more restrictive provisions in the original bill were amended also because of pressure from patient groups afraid that research to their benefit would be hampered by the proposed consent system.

Wendler emphasises autonomy and argues that one-time consent protects the autonomy of individuals and protects them from serious risks. There are two major arguments against this. Firstly, autonomy should be balanced against other values such as the interests of patients who might benefit from this research.[4] Secondly, autonomy as such cannot protect individuals from risks but only from risks they do want to carry. Research on residual tissue, whether anonymous or anonymously used and being coded, does not carry any risks to individuals. Ethical review boards should oversee that sufficient measures have been taken to ensure that the samples used in research remain anonymously used. It should be possible to enrich data from tissue research with patient data. Fully anonymising samples, as suggested by Wendler, is a waste of valuable information.[5]


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Good idea, but will it happen?

Editor—Wendler's advocacy of one-time consent for research use of biological samples that would otherwise be discarded as clinical waste is welcome and would be ethically sound and financially efficient.[1] But this suggestion is not new. The Royal College of Pathologists advocated exactly this five years ago, at the height of the organ retention controversy, stating that in relation to tissue removed from living patients: "we suggest that as a minimum it should be possible to record consent or objection to 'generic' research use, as outlined above, and to teaching and quality control. Consent or objection should be assumed to refer to all samples from that patient, unless otherwise specified."[2]

However, the college also stated that it was "gravely concerned about implementation, and the speed at which it will occur. We believe it highly unlikely that NHS trusts will act with sufficient urgency . . . We therefore urge the Departments of Health to distribute appropriate instructions."

Since then the introduction of the Human Tissue Act 2004 puts the onus on researchers to obtain consent, even for tissue, blood, and urine which would otherwise be disposed of as waste, even though the patients concerned have usually gone home long before the need for consent is recognised. The act does permit the use of tissue in research without consent, but only if samples are anonymised (which makes crucial clinical correlation difficult or impossible) and if a research ethics committee has approved (and experience suggests that many such committees will regard this as inappropriate and demand consent anyway).

The college showed that to ask for consent every time a sample is taken would be absurdly expensive and that staff not involved in research would not do it. So it argued for one-time consent during the development of the act—without success. It is not part of the act. It has not been advocated by the Department of Health or (yet) by the new Human Tissue Authority. But no workable alternative has been proposed.

As Wendler shows, the autonomous wish of the vast majority of patients is that their surgical waste should be available for the benefit of mankind, rather than being incinerated. At present, most patients are never asked, so this wish is ignored.

Failing to ask empowers no one. Is such disrespect for patient autonomy not an ethical outrage?

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Autonomy and majority rules have been misunderstood

Editor—Wendler suggests that since most (79-95%, depending on the study) people were willing to provide a one-time general consent to further usage of their biological sample we should routinely include a request for the subject to consent to the further indefinite usage of their samples in consent forms and participant information sheets.[1]

This misconstrues the nature of autonomy by conflating it with majoritarian democracy. Simply because most people would hypothetically consent to something does not mean doing that thing is part of respecting autonomy.

Autonomy is about respecting the individual's right to choose for himself or herself—typically taken to be the basis for the requirement of informed consent.[2] Its two elements are having sufficient information to make the decision well, and being competent to make that decision.

This seems to require full and appropriate information about what will be done with the samples. Thus the real debate ought to be whether a one off indefinite consent can genuinely be considered to be valid consent. Is consent given in these circumstances genuine consent? This debate matters from the point of view of autonomy, not whether people are happy to give their consent.

Imagine if a researcher presented a medical study asking participants to participate without telling them what was being studied.

In almost any other circumstances we would not accept as competent someone who consents to participate in research without knowing what is being studied or what the expected or hoped for outcomes are. There seems no reason to believe that people are more competent to decide what should happen to their biological samples, without any knowledge of what is being done with them.

Finally, implicit in the high rate of consent for indefinite research may be that people tacitly understand the research to be only for medical purposes. The rates of consent are likely to plummet if it was pointed out to participants that their blanket consent could lead to their samples being used to develop chemical or biological weapons, to take an extreme example.

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Harmful impact of EU clinical trials directive

Trial of alerting drug in fibromyalgia has had to be abandoned . . .

Editor—Hemminki and Kellokumpu-Lehtinen show the impact of the EU Clinical Trials Directive and the resulting additional cost and bureaucratic delays on cancer drug research.[1] It has become almost impossible for academic researchers to initiate and conduct pharmaceutical trials without the involvement of a pharmaceutical company, particularly in areas that do not attract much funding or involve a drug that is close to the end of or outwith patent protection.

We recently abandoned attempts to conduct a trial of an alerting drug in patients with fibromyalgia. The Trials Directorate of the Medicines and Healthcare products Regulatory Agency (MHRA) was as helpful as possible within the limits of the regulations, but the cumulative burden of regulatory requirements and delays, both locally and nationally, resulted in the modest grant from the pharmaceutical company being almost exhausted before we could even begin to contemplate the recruitment of a single patient.

We endorse the authors' plea that these regulations, and their national implementation, are harming the very group they were designed to protect, and should be amended as a matter of urgency.

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1 Hemminki A, Kellokumpu-Lehtinen P-L. Harmful impact of EU clinical trials directive. *BMJ* 2006;332:501-2. (4 March.)

. . . and so has trial of melatonin in cancer related weight loss . . .

Editor—The editorial by Hemminki and Kellokumpu-Lehtinen on the harmful impact of the EU Clinical Trials Directive highlights important issues that need to be addressed before investigator led cancer research becomes a thing of the past.[1] The directive was supposed to protect patients by minimising biasing influences on clinical studies. The reality is that it has made it all but impossible to carry out researcher led studies without the financial and logistical backing of the pharmaceutical industry.

We recently successfully negotiated the new and long EU research directive road, through the process of clinical governance, sponsorship, and ethics approval to run a double blind placebo controlled trial of melatonin in cancer related weight loss. Unfortunately, after 18 months our research quest had to be abandoned because the directive decreed that we needed to have an investigational medicinal product licence. This was not stipulated at the start of the process.

Without the support of a pharmaceutical company we were unable to secure such a licence. Presumably the potential for profit from a cheap product such as melatonin is limited. I suspect that other researchers looking to investigate medicinal products for which there may be limited commercial potential may meet similar difficulties. This poses the question: by trying to improve the quality of clinical research and safeguard patients, how much bias has the EU directive introduced to clinical studies to the detriment of the same patients the directive is supposed to be safeguarding?

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. . . while paediatric oncology is being scuppered

Editor—The editorial by Hemminki and Kellokumpu-Lehtinen is a startling summary of the impact of the EU Clinical Trials Directive and the associated national legislation on the conduct of investigator led research.[1] It is remarkable how little response or debate has emerged since the introduction of this directive: every investigator with whom I have discussed its impact complains about increasing bureaucracy and associated costs.

Paediatric cancer, by its nature, involves only small numbers of patients and relies almost exclusively on investigator led trials. Over the past few decades, there have been major advances in the outcomes for children with leukaemia and Wilms' tumour, to choose but two conditions. In the past nearly all children in the United Kingdom with such conditions were included in a clinical trial. Now, however, the financial and administrative burden that has recently been inflicted is beginning to erode the traditionally high rates of recruitment to paediatric cancer trials. Should this process continue it will become impossible to complete such trials in a timely fashion and treatment will cease to evolve.

If the goals of the EU Clinical Trials Directive were to improve the protection of patients, the reliability of research reporting, and to harmonise and increase the competitiveness of European clinical research, the directive is clearly failing to achieve any of its stated objectives. And further directives are to be expected. All of us involved in investigator led research of this type need to lobby our representatives to have the current legislation amended.

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Who will fund hypothesis testing studies?

Editor—Although Loke et al concluded that case reports in pharmacovigilance have limited value,[1] case reports or series are valuable as hypothesis generating papers, which benefit clinicians and patients. The number of follow-up studies is only one outcome by which to judge the value of case reports or series, but other outcomes may be more difficult to study.

Although case reports are valuable in pharmacovigilance, hypothesis testing studies are necessary and I agree with Vandenbroucke that a more consistent scheme is needed.[2] An important question is, where will funding for such studies come from? Pharmaceutical companies may have little incentive to further investigate adverse reactions and if funding is provided there may be conflicting interests. For different reasons, governments may also be reluctant to fund pharmacoepidemiology studies.[3]

In New Zealand, the government funded intensive medicines monitoring programme (IMMP) performs hypothesis-testing studies which further investigate adverse drug reactions, including calculating incidence and identifying patients at risk.[4] The programme was established in 1977, when it was recognised that spontaneous reports were insufficient to detect and fully evaluate adverse drug reactions. In its almost 30 year history, the programme has performed many valuable studies and is internationally respected,[3] yet its future remains uncertain. None of the staff has a contract beyond 30 June 2006. It is still not known how the programme will contribute to the new Australia New Zealand Therapeutic Products Agency (www.tgamedsafe.org). In the meantime, important pharmacoepidemiology studies are at risk of not being completed, with loss of valuable data contributed over many years by patients and doctors throughout New Zealand. The agreement that hypothesis testing studies are required as a component of pharmacovigilance must be backed by a commitment to fund such work adequately.

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LIFT study is discontinued

Editor—We informed the *BMJ* about the increased risk of stroke in the long term intervention on fractures with tibolone (LIFT) study.[1] Further analysis now indicates a benefit of tibolone on risk of vertebral fracture, the primary end point of the study. Thus, the LIFT study is being stopped because of a recommendation by the data safety monitoring board that the trial has reached its objectives and additional follow-up is unlikely to provide further information about other adverse events.

LIFT is a randomised clinical trial designed to determine the effect of treatment with tibolone on risk of vertebral fracture in postmenopausal women with osteoporosis. Altogether 4538 postmenopausal women with a bone mineral density T score at the total hip or spine equal or lower than −2.5 without a fracture or a T score of −2.0 with a fracture were assigned to 1.25 mg tibolone or placebo. The average age of participants was 68 (SD 5.2) years. They are followed up periodically for clinical outcomes and safety. The trial started in 2001 and the primary outcome analysis is scheduled for June 2006.

A data safety monitoring board periodically reviews the unblinded results. A steering committee, whose voting members are investigators independent of the sponsor, Organon, oversees scientific issues. The data safety monitoring board has previously notified the sponsor and steering committee of an increased risk of stroke during an average of 2.4 years of the trial with a hazard ratio of 2.591. The updated results (at 2.75 years) for stroke (ischaemic plus haemorrhagic) and vertebral fractures (based on a semi-quantitative reading of the radiographs) for tibolone and placebo groups were respectively 25 (1.11%) and 11 (0.49%) (hazard ratio 2.3 ($P=0.02$)) and 44 (2.1%) and 85 (4.1%) (hazard ratio 0.5 ($P=0.0003$)).

The data safety monitoring board has recommended to us that the study be discontinued and that dispensation of all study treatments to subjects be ended as soon as practicable. We have concurred and plan to publish a more detailed report.

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1 Grobbee DE, LIFT Steering Committee. LIFT study to continue as planned. *BMJ* 2005;331:843.

Stress and illness: call to action

Editor—The prospective study by Chandola et al on chronic stress at work as a risk factor for the metabolic syndrome adds a further public health imperative to reduce the significant morbidity from chronic stress at work.[1]

Last month a BUPA insurance survey found that seven million Britons feel so ill with "worry" that they seek medical help.[2] In the employed population the British Occupational Health Research Foundation found that the largest, and growing, cause of work related ill health is now mental ill health.[3]

A number of remedial interventions such as cognitive behaviour therapy have been looked at, generally in individual sick employees. In terms of the social gradient of illness described among civil servants,[1] individual interventions worked best with employees in high-control jobs.[3] Employers have a legal duty of care to protect the health of all their employees, and the Health and Safety Executive has published management standards aiming to reduce stress at work.[4] In terms of reducing chronic stress, it may help to consider change at the level of positive wellness for the whole organisation, perhaps using a social engagement model with dynamic learning-in-action.[5]

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1 Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ* 2006;332:521-4. (4 March.)
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Alcohol use disorders identification test has bias

Editor—In the brave new world of a National Health Service where value for money is tantamount, Coulton et al are to be commended for using several valid clinical outcome measures for alcohol misuse and dependence and comparing them with more traditional biochemical variables commonly used in both primary and secondary care.[1] However, some caution is required in interpreting their results in light of the methodology.

Firstly, the alcohol use disorders identification test (AUDIT) is made up of questions that assess aspects of alcohol use such as quantity or frequency and dependence. Therefore its internal validity when measured against outcomes such as binge drinking and alcohol dependence is likely to be high in ROC (receiver operating characteristic) analyses. A more clinically meaningful outcome for primary care may be the presence of problems consequent on drinking, which could have been ascertained using a rating scale such as the drinking problems index.[2]

Secondly, the selection of male drinkers is a major source of bias, as traditional screening tools such as AUDIT show low sensitivity in detecting alcohol misuse in women and older people.[3 4] The study by Coulton et al would need further replication in both these populations, as well as in inner city areas, where populations show greater cultural diversity.

Although this paper was an important contribution to detecting and screening alcohol use disorders in primary care, clinicians should be mindful of the wider population, or the general public may be misinformed in the same way as it was with the public health message of alcohol and cardioprotection, which, again, only applies to a section of the population.

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Competing interests: None declared.

1 Coulton S, Drummond C, James D, Godfrey C, J Bland JM, Parrott S, et al. Opportunistic screening for alcohol use disorders in primary care: comparative study. *BMJ* 2006;332:511-7. (4 March.)
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Where patients with cancer die in Cuba

EDITOR—Gomes and Higginson show that identifying the factors influencing where terminally ill patients with cancer die is complicated.[1]

In 1981-2 we studied 13 105 deaths in adults (≥15) in three different Cuban provinces. Only 27.0% of adult deaths due to malignant tumours occurred outside hospitals in Ciudad de La Habana, a western province that includes the capital of Cuba, compared with 60.2% in Cienfuegos, in the centre and southern part of the island, and 58.2% in Las Tunas, in the eastern side. The people who died at home were older than those in hospital, were found less in urban areas, and showed no variation by sex.[2]

We then studied adult mortality in the same three Cuban provinces over 10 years from 1990 to 1999. There were 36 999 deaths due to malignant tumours in Ciudad de La Habana (19.3% of all deaths), 5269 in Cienfuegos (19.9%), and 5820 in Las Tunas (21.6%). The mean ages were 67.9 (14.6) years, 67.9 (15.9), and 66.1 (16.6), respectively. Only 28.3% died at home in Ciudad de La Habana compared with 61.8% in Cienfuegos and 34.4% in Las Tunas.[3]

We recently carried out another study in Cienfuegos City, the capital, to investigate why so many more patients with cancer die at home in Cienfugos (unpublished data). We interviewed the relatives or proxies of a randomised sample of 226 adults (≥15) who had lived in the city and died in 2003. Of 171 who were classified as terminally ill, 91 (53%) had died at home—in 58% of cases because of the patient's or relatives' choice.

For the last years of the past decade we have implemented a comprehensive programme of palliative care in primary care in Cienfuegos. The high proportion of deaths at home in patients with cancer could be related to this new service.[4] Even in a highly organised national health system such as Cuba's—universal, accessible, equitable, and free to all—looking for local answers to specific conditions seems to be effective.[5]

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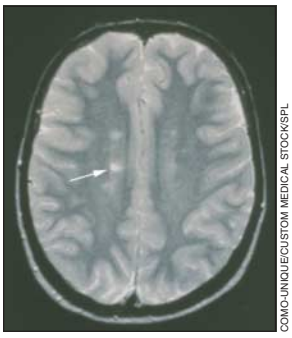
Diagnosis and treatment of multiple sclerosis

Potential changes in management for clinically isolated episode of optic neuritis

EDITOR—Murray highlights the recent advances in diagnosis and management of multiple sclerosis.[1] This is particularly important in managing a clinically isolated episode of optic neuritis. Current UK ophthalmological management of a unilateral episode of typical optic neuritis is generally not to investigate or to treat.[2] However, with the development of the McDonald criteria for diagnosing multiple sclerosis and advances in magnetic resonance imaging of lesions,[3 4] there is potential for early diagnosis of multiple sclerosis.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This is important as new treatments such as recombinant interferon beta-1a may reduce the development of clinically definite multiple sclerosis.[5] Future best clinical practice in the management of acute optic neuritis may therefore be to investigate all patients to identify those with multiple sclerosis who would benefit from early treatment.

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Ocular manifestations of multiple sclerosis

EDITOR—Murray reviewed the diagnosis and treatment of multiple sclerosis.[1] Ocular manifestations are sometimes the first sign of the disease, including optic neuritis, internuclear ophthalmoplegia, ocular motor cranial nerve palsies, trigeminal and facial nerve palsies, nystagmus, pars planitis, and retinal periphlebitis.[2] These conditions may predict additional demyelinating events.

The optic neuritis treatment trial is a randomised 15 centre trial of 457 patients to assess the effects of corticosteroids in optic neuritis.[3 4] The results showed that intravenous methylprednisolone hastened the recovery of visual function after optic neuritis without significantly improving the long term final visual acuity. The trial also showed that while intravenous steroids reduced the incidence of symptomatic multiple sclerosis, oral steroids were associated with an increased recurrence of optic neuritis.

The treatment of intermediate uveitis due to multiple sclerosis is indicated when the visual acuity is 6/12 or less due to cystoid macular oedema. This includes systemic and posterior sub-Tenon steroids, cryotherapy, and pars plana vitrectomy.[5]

Symptomatic patients with longstanding ocular motility disorders and ocular cranial nerve palsies may benefit from prisms or corrective surgery on extraocular muscles.

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Postnatal economic burden of limited karyotyping

EDITOR—Chitty et al suggest a strategy to identify chromosomal abnormalities that relies on quantitative fluorescent polymerase chain reaction (qf-PCR) and full karyotyping only in cases of fetal nuchal translucency thickness > 4 mm, as opposed to full karyotyping of all chorionic villous samples.[1] Eliminating double testing results in an upfront economic savings of about £1.5m (€2.17m; $2.50m) distributed across 17 479 pregnancies. However, such an

approach has a failure rate of 1%, the economic consequences of which Chitty et al do not appreciate in their discussion.

The incremental lifetime economic cost incurred by an infant born with trisomy 21 is about £350 000 (adjusted for 2006 currency).[2] Considering only chromosomally abnormal babies that came to term as well as those undetected by limited karyotyping, and given a reasonable termination rate of 70%, the six babies that would have been missed in the study alone represent an economic cost of £2.1m.

Assuming 640 000 yearly births in England and Wales,[3] and the necessity for chorionic villous sampling in about 6% of pregnancies,[4] we estimate that a shift from full karyotyping to the approach suggested by Chitty et al will result in a systemic economic loss of over £5.3m (that is, incremental costs of infants born with trisomy 21 minus savings from limited karyotyping) each year. This is not to ignore the externalities and intangible costs that may be brought about by missed cases of chromosomal abnormality. It may be worth shouldering upfront testing costs to provide truly accurate information to mothers, and avoid much greater subsequent societal economic burden.

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Competing interests: None declared.

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Physiological-social scoring is important in pandemic flu

Editor—Barlow argues that prognostic assessment will be important in a flu pandemic.[1] Although the predictive tools CURB-65 and CRB-65 have been validated in terms of 30 day mortality,[2] their limitations with respect to prediction of mortality have recently been highlighted. Their value as a track and triage tool has not been established.

This is of prime importance as the numbers of presentations expected during a flu pandemic require that an instrument be developed which recognises the physiological derangement and social and comorbid factors which normally influence hospital admission criteria. Ideally, this tool would be applicable across the health economy and amenable to use in primary and secondary care by medical, nursing, and allied health professionals.

Given the magnitude of a pandemic (we calculate that attendances at our emergency department may be in excess of 600% of normal[3]), it is imperative that any clinical guidance recognises that degradation with scale will occur as the pandemic progresses. We therefore suggest that any triage tool should be scalable in terms of admission threshold.

Using the principle that physiological parameters deteriorate for several hours to days before catastrophic decompensation, we suggest that a modification of the previously published medical early warning score will provide a useful triage tool to identify those in need of admission and reassure those fit to self care at home.[4] The modification addresses comorbid and social factors. We discuss the validation of our tool in the *European Respiratory Journal*.[5]

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GPs provide valuable continuity during age transition

Editor—We support the key elements of transitional care between adult and paediatric care advocated by McDonagh and Viner.[1] However, they did not discuss the role of the general practitioner (GP) in managing chronic illness during and after transition. General practitioners play a central part in coordinating care after transition and are well placed to help provide continuity of care.

We conducted a small survey of carers of people with profound and multiple learning disabilities in Scotland. Carers were noticeably more dissatisfied by care on transition to adult services, failure of coordination of care being a central factor. In our follow-on survey of general practitioners in Lothian 65 of the 100 who responded to the questionnaire thought that they did not have adequate training to assess and treat people with profound and multiple learning disabilities, and 63 thought that they would benefit from additional training.

With an ever increasing number of general practitioners with special interests in specific chronic diseases, the possibility of training general practitioner specialists to help manage transition and beyond is appealing. We found an encouraging number of general practitioners (16 of those who replied) were interested in undergoing such specialist training.

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Competing interests: None declared.

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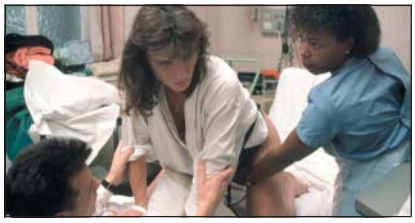
The importance of being naked from the elbow down



SALLY GREENHILL

Editor—In the neonatal intensive care unit we demand that all staff remove their jewellery at the beginning of each shift. Anyone wearing a watch or dress ring is deemed not to have washed his or her hands. "Naked from the elbows down" is the expression in common usage. Visiting surgeons and all other disciplines now comply with our regulations.

It was therefore with some disappointment that I viewed the cover photograph of the *BMJ* of 4 March showing a mother squatting in labour (above).[1] The midwife's watch on her left wrist is disappearing into the groin of the labouring woman.

When will we take this subject seriously?

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1 Cover. Inducing labour at term. *BMJ* 2006;332 (7540). (4 March.)

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