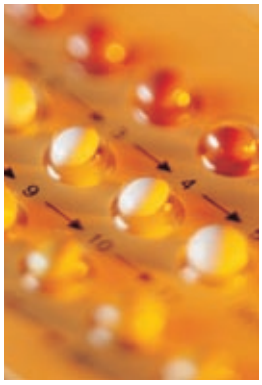
Risk of cancer and the oral contraceptive pill

Long term follow-up of women in the UK shows no increased risk



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In the preface to the first comprehensive publication from the Royal College of General Practitioners' oral contraception study Sir Richard Doll wrote, "Final judgement on the safety of the pill must still await the passage of time, when observations can be made of women who have used the pill for 10 or 20 years."[1] Thirty years later, in this week's *BMJ*, Hannaford and colleagues[2] report incidence rates of cancer in relation to use of the pill among women in the study cohort.

Between 1968 and 1969, 45 950 women in the United Kingdom were enrolled in the study, and they were followed for a mean of 24 years. Full assessment of the risk of cancer needs a long follow-up as effects of the pill may persist many years after its use has been stopped. Incidence rates of cancer in women who ever used the pill were compared with rates in women who never used the pill. On balance, no higher risk of cancer was found in pill users. Risks were significantly lower for cancer of the colon or rectum, uterine body, or ovaries; the main gynaecological cancers combined (uterine body, ovaries, cervix); and for any diagnosis of cancer. The incidence of breast cancer was similar in pill users and never users.

These data came from six monthly reports from the women's general practitioners until 1996, and from linkage of the 35 050 women still in the study in the mid-1970s to National Health Service central registries. These provided cancer diagnoses until 2004 to supplement those reported by general practitioners. The follow-up covered two thirds of the woman years that would have accumulated if all 45 950 women had been followed from 1968 or 1969 to 2004.

Hannaford and colleagues also report analyses restricted to follow-up by general practitioners until 1996, which allow incidence rates to be calculated according to duration of pill use and time since stopping use of the pill. The comparisons between ever users and never users were largely similar for the two sources of data. After adjustment for age, parity, smoking, social class, and use of hormone replacement therapy, the relative risks of cancers of the ovary and uterine body in ever users compared with never users were below unity for all durations of pill use (≤48, 49-96, and ≥97 months). The opposite was found for cancers of the cervix and the brain or pituitary—relative risks increased progressively with longer use. The patterns of risks by time since stopping the pill were largely reassuring, although some excess risk of cervical cancer persisted 10-15 years after stopping, and risk of brain or pituitary cancer persisted 20 or more years after stopping. Some individual risk estimates are significantly different from 1.0; for example, risk of breast cancer was increased 15-20 years after stopping, yet was significantly reduced 20 or more years after stopping. Considering the many comparisons included in the paper, individual risk estimates must be interpreted with caution.

The data from this and other studies indicate that pill use prevents or postpones ovarian and endometrial cancers[3 4] but probably accelerates development of cervical cancer caused by chronic infection with oncogenic human papillomavirus.[5] Fortunately, preinvasive cervical cancer can be detected by cervical cytology and treated. Regular cervical cytology screening remains an important element of quality health care, particularly for women who use the pill.

The finding that pill use increases the risk of brain or pituitary cancers may result from prescription bias—menstrual disturbances are often regulated by the pill, and such disturbances may be an early symptom of pituitary disease. One study of pituitary prolactinomas and pill use found odds ratios of 7.7 (95% confidence interval 3.5 to 17.0) in women prescribed the pill for treatment of menstrual irregularities and 1.3 (0.7 to 2.6) in women prescribed the pill for contraception.[6]

Considering that the Royal College of General Practitioners' study enrolled women almost 40 years ago, the age distribution of pill users is remarkably similar to current patterns of use. At enrolment, 61% of pill users were under 30 years, and the age group 20-24 years had the largest number of women.[1] A UK survey in 2005-6 showed that 52% of pill users were under 30 and the highest prevalence of pill use was among 20-24 year olds.[7]

Pills used in the late 1960s and 1970s contained higher dosages of progestogens and oestrogen (ethinylestradiol) than the currently widely used 30 μg ethinylestradiol combined pills. Pill users in the study would have started with higher dose pills, with a progressive switch to the lower dose formulations used today. Limited data suggest that the reduced risks of ovarian and endometrial cancers are maintained with lower dose pills, so that the overall balance of cancer risks can be expected to apply to today's pill users.

The results of this unique long term study agree with findings from the Oxford Family Planning Association's cohort study and modelling studies.[3 4] The results show that—in a developed country with an effective cervical cancer screening programme—the pill is a safe contraceptive method with respect to cancer. In some developing countries—with inadequate cervical cancer screening and healthcare services, and high cervical cancer rates—the balance of cancer risk is probably less favourable.[8] However, in such settings, contraceptive benefits must be weighed against the risk of cervical cancer, and the balance would tilt in favour of the pill because of the high morbidity and mortality associated with unplanned pregnancies.

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New methods of analysing cost effectiveness

Value of information analyses must be integrated into the process of commissioning primary research

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Interest in whether health interventions are value for money as well as effective has meant that the term cost effectiveness[1] is commonly used (and sometimes misused) in the clinical literature. Consequently, methods for determining cost effectiveness have been refined, especially techniques for synthesising evidence and representing uncertainty in the results of such evaluations. Techniques such as multi-parameter evidence synthesis[2] and value of information analysis[3] are now routinely integrated into cost effectiveness studies, especially health technology appraisals (HTAs) conducted for the National Institute for Health and Clinical Excellence. But is there real value in the development and application of such techniques, or have these new methods emerged simply as a consequence of involving academics in the process of evaluation?

In this week's *BMJ,* Colbourn and colleagues present a cost effectiveness and value of information analysis of strategies for preventing group B streptococcal and other bacterial infections in early infancy.[4] This is a timely assessment of the potential cost effectiveness of various ways of organising a national screening programme for group B streptococci, which can influence UK policy on whether (and how) to implement such a screening programme. However, what do the sophisticated techniques used add to what we already know about the effectiveness and cost effectiveness of preventive strategies for this infection?

Firstly, the techniques of decision analysis combined with multi-parameter evidence synthesis allow a comprehensive assessment of all of the evidence that relates to the policy question, including the consideration of all possible strategies (something Colbourn and colleagues have taken to the extreme, with 341 strategies evaluated in this paper alone). This contrasts with the Cochrane review approach, which typically uses only randomised evidence to assess a single treatment comparison.

In addition, a probabilistic analysis of uncertainty in the parameters of the model allows a full assessment of the implication of the estimated uncertainty for the decision. This means the analysis can answer two fundamental questions relating to the choice between the strategies evaluated. Firstly, on the basis of the existing evidence, what is the preferred course of action? Secondly, should additional information be collected to better inform that decision?

The analysis by Colbourn and colleagues shows that, on the basis of existing evidence, it is likely that immediate changes to the organisation and delivery of services to prevent group B streptococcal infection would greatly benefit the health service. Furthermore, given the size of the population concerned, it highlights the value of further research, particularly into the potential use of an intervention (vaccination) that is not yet available in the United Kingdom. However, as the authors point out, even though further research may be valuable this does not mean that the proposed trial of screening for group B streptococci, at an estimated cost of £12m (€18m; $24m), is the correct way forward. Indeed, the analysis suggests that the screening strategies proposed as comparators in this trial are unlikely to be cost effective.

In the absence of an available vaccine, the value of additional evidence currently lies elsewhere—particularly in resolving the choice between intravenous and oral drugs for certain preterm infants. It is unfortunate that the two teams responsible for the synthesis of evidence[5] and the design of a clinical trial, both funded by the HTA programme, seem to have worked independently and concurrently. The value

of comprehensive evidence synthesis and value of information analysis is to inform the design of further research studies.

The Cooksey review called for an expansion of the National Health Service HTA programme "to enhance the evidence base informing decisions on the effectiveness and cost-effectiveness of technologies in the NHS,"[6] while recognising the need from the outset to "develop a system of metrics that can accurately evaluate the impact of this expansion."[6] Value of information analysis, by seeking directly to investigate the potential returns to further investment in research, offers exactly this metric. However, for it to fulfil its full potential, it must become an integrated part of the process of commissioning primary research.

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Effectiveness of chest pain units

Trial shows no benefit overall, but success may vary as a result of operational factors that are difficult to measure

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Acute chest pain is responsible for one in four emergency medical admissions in the United Kingdom,[1] and these figures are probably similar in most Western countries. People with chest pain are rightly encouraged to seek help early, and attendances to emergency departments are rising. Emergency departments are responsible for quickly identifying and treating people with acute myocardial infarction and unstable angina, and for evaluating people with a lower likelihood of acute coronary syndrome.

Identifying which patients at low risk of acute coronary syndrome can be safely sent home and which patients need further observation and investigation is not easy, especially when the consequences of misdiagnosis include infarction, arrhythmia, and death. The strategy of evaluating such patients in a chest pain unit based within or near the emergency department is used in 30% of emergency departments in the United States.[2] The practice is supported by randomised trials that studied particular risk groups and methods of diagnosis, and in healthcare settings specific to the US, so the results may not be generaliseable elsewhere.[3-5] In theory, a chest pain unit should improve outcomes—but does it?

In this week's *BMJ*, a cluster randomised controlled trial (effectiveness and safety of chest pain assessment to prevent emergency admissions; ESCAPE) by Goodacre and colleagues tries to answer this question.[6] It follows on from the encouraging results of a previously reported single centre randomised trial, which found that a chest pain unit reduced hospital admissions and health service costs.[7]

The ESCAPE trial enrolled 14 hospitals, seven of which had a chest pain unit. The trial defined low risk patients as those with chest pain possibly as a result of acute coronary syndrome, but who had no new electrocardiographic changes diagnostic of the syndrome or prolonged or recurrent cardiac-type pain. In people admitted to hospitals with a chest pain unit, serial electrocardiography was performed over two to six hours, biochemical markers were measured, and an exercise treadmill test was typically performed the next working day. People admitted to hospitals without a chest pain unit received the usual service typically consisting of admission for troponin measurements over 12 hours, with no early exercise testing.[8] The outcomes were measured the year before and the year after either the introduction of the chest pain unit or continuance of the same service. The introduction of a chest pain unit had no significant effect on the proportion of people attending the emergency department with chest pain, the proportion of people with chest pain who were admitted, or the number of people admitted over the next 30 days. However, a small increase was seen in the proportion of patients reattending (odds ratio 1.10, 95% confidence interval 1.00 to 1.21, P=0.036) and in the number of daily medical admissions (1.7 per day, 0.8 to 2.5, P<0.001).[3]

Setting up a chest pain unit led to more patients being tested, but no reduction in the proportion of patients admitted. Why was this? Perhaps different staffing levels and opening hours reduced the impact of the chest pain unit—this might partially explain the variation in the proportion of adult attendances managed in these units (1-7/1000 attendances at the emergency department). The variation in the average age, risk factors, and known coronary heart disease between the chest pain units suggests that some patient selection occurred.[8] Why was there no effect overall even though some chest pain units worked well? Perhaps factors that determine the success of a service (such as enthusiasm of the staff, buy in by other relevant specialties) are difficult to measure in a trial setting. Clearly, one size does not fit all, and how

these services fit within the wider context of health care is important.

Patients expect serious disease not to be missed, and unless hospitals are explicit about what risks they are prepared to accept and pay for, clinicians will use whatever tests and periods of observation they can to rule out serious disease. The failure of this trial to show a benefit of chest pain units does not reduce the need to find and implement a diagnostic strategy to discriminate in this growing low risk patient population between patients with a low likelihood of an adverse outcome related to the acute coronary syndrome—who can be safely discharged—and those who need further treatment or inpatient evaluation. Future studies need to focus on the successful implementation of a new diagnostic service and where possible how such testing can be simplified.

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The Declaration of Helsinki

Mosaic tablet, dynamic document, or dinosaur?

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The Declaration of Helsinki is a respected institution and one of the most influential documents in research ethics,[1 w1-w7] having withstood five revisions and two clarifications since its conception in 1964. Its guardian, the World Medical Association, recently invited submissions for further revision.[2]

The history of the declaration has been well documented.[3-5] The Nuremberg Code (1947) was one of the first statements of the ethical principles involved in human experimentation.[w8] However, because of its association with Nazi war crimes it had relatively little effect on practice.[w9] The Declaration of Helsinki dealt with clinical research more directly, but was portrayed as a weakening of the stringent protections of Nuremberg. Nevertheless, for a quarter of a century only minor changes were made and it became engrained in the international culture of research ethics.

In 1996, the declaration added a reference to placebos in response to concerns about trials in perinatal HIV transmission in developing countries**.** Critics pointed out that continuing to use placebos when efficacy had been demonstrated implied a different ethical standard for developing countries than for developed ones. Having entered into the specifics of trial design the declaration was drawn into a debate on whether ethical principles are universal or are relative to the context in which they are applied[6] and also into related principles of research in developing countries.

The World Medical Association was then pressured to make more radical reforms. An American proposal, seen by some as a further attempt to weaken the declaration, resulted in a vigorous debate, but despite lack of consensus and strong feelings by some that it should not be changed,[7] a major revision was approved in 2000. This did little to improve acceptance.

Concerns were also expressed that the cumulative changes represented a shift towards protecting the efficiency of research at the expense of the protection of human subjects. A division between developed and developing countries also emerged with claims of American ethical imperialism,[6 8 w10] although new emphasis on social justice and a duty to benefit communities as well as individuals received praise. Complaints about clarity resulted in the addition of footnotes in 2002 and 2004, but this also failed to achieve global endorsement. The situation was further complicated by the appearance of other guidelines, including those from the Council for International Organizations of Medical Sciences,[w11] the Nuffield Council,[w12] and Unesco (United Nations Educational, Scientific, and Cultural Organisation),[w13] which were seen to be potentially conflicting. It was even suggested that the declaration was out of touch and irrelevant.[9]

The debate on the future of the declaration raises several fundamental questions about the essential purpose of the declaration, its structure (basic principles or procedural rules), its status (static or dynamic), the extent to which it can influence understanding and practice, and the nature and limits of universality in ethics.

The nature of the declaration has progressively changed from simply restating Nuremberg as an ethical code to being increasingly prescriptive.[10] The more procedurally based it has become the more divergent opinion has become, with calls for reversion to the simplicity and conciseness of a Nuremberg-like document. Other guidelines by contrast provide detailed commentaries, and the declaration may fail by being neither code nor commentary. The arguments surrounding the declaration point to a failure to clearly separate related but distinct concepts—standard of care, ethical standards, ethical principles, and the operationalisation of principles.

Whether "ethical standards" are considered universal will depend on what exactly is meant by this term. They have been criticised as representing the North

American context in which they were formulated.[11] The more that basic principles are elaborated, the more room there is for interpretation and dissent.

Among core ethical principles, respect for the individual's autonomy and their community have traditionally been considered the most important. The principle of autonomy has recently undergone much rethinking. Autonomy should not be thought of as always completely free of external influence, but to be relational, constrained by factors such as health, social relationships, sex, and power inequality.[w14] The debate has occurred within too narrow a formal framework, without sufficient attention to the inherent inequalities and vulnerability that characterise the relationship between subjects and researchers. It requires reframing by stating that respect for the individual needs to encompass both their individuality and the cultural and relationship factors that shape their decision making.

The World Medical Association needs to respond to criticisms that a lack of transparency in its revision process does not reflect the spirit of openness and disclosure in articles 11, 16, and 27 of the declaration. Similar considerations of transparency should apply to all aspects of the conduct and results of research itself, as described in the Ottawa Statement (ottawagroup.ohri.ca/index.html).

The declaration has only limited direct legal authority[1] but has gained considerable moral authority. As such it is more symbolic than instrumental. Symbolic function is evident by people's attitude towards it, and the frequency with which they use it to justify their opinions. Its instrumental role derives from direct reference in legal statutes, and indirectly through influence on legislators and courts.[1]

It is difficult to estimate how effective the declaration is. Claims that it is violated daily raise questions as to how effective it can be in the absence of monitoring or enforcement. However, a complete understanding of the role of the declaration requires us to recognise that it represents an external imposed morality, not the researcher's own internal morality,[w15] which limits its ability to influence practice. Ethical research is a collective responsibility. Unless researchers incorporate the ethical principles outlined by codes such as Helsinki into their own and the collective morality[12] they will remain simply words. The Declaration of Helsinki is a brave venture and "the property of all humanity,"[4] which has the potential to continue to promote high ethical standards and protect the vulnerable, but only if we embrace it. The declaration's strength lies in its core principles, which are a moral compass transcending procedural rules and revisions.

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Extra references [w1-w15] are available on bmj.com

Physician assisted death in vulnerable populations

Claims of increased risk in these groups are not supported by evidence

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Physician assisted death (both voluntary active euthanasia and physician assisted suicide) has been openly practised in the Netherlands for more than 25 years and formally legalised since 2002. The practice has been analysed in four major national studies between 1990 and 2007.[1 2] A more restricted form of physician assisted death (physician assisted suicide only) was legalised in Oregon in 1997 and is the subject of an annual report (www.oregon.gov/DHS/ph/pas/index.shtml). Although these studies do little to resolve the moral and religious questions surrounding these practices, they do answer the following questions about the risks and benefits of legalisation.

Will these practices become more common over time in a permissive environment? In Oregon, physician assisted death accounts for around one in 1000 deaths each year, with no significant change in frequency over nine years. All patients have met the necessary criteria, and more than 85% were also enrolled in hospice programmes. In Oregon, one in 50 dying patients talk to their doctors about assisted death and one in six talk to family members.[3] There seems to be much conversation about end of life options, therefore, but relatively few cases of assisted death. Oregon is among the nation's leaders in other markers of good end of life care, including deaths at home, opioid prescribing, hospice enrolment, and public awareness about end of life options.[4] The Dutch practices of physician assisted death have also remained stable over the duration of four studies,[2]

and hospice and palliative care have become more prevalent in recent years.

Will the burdens and risks of these practices fall disproportionately on vulnerable populations? A study by Battin and colleagues published in this week's *Journal of Medical Ethics* that analyses existing databases from Oregon and the Netherlands dispels many of these concerns.[5] They found no increased incidence of physician assisted death in elderly people, women, people with low socioeconomic status, minors, people in racial and ethnic minorities, and people with physical disabilities or mental illness. The one exception was people with AIDS, and studies from San Francisco completed before protease inhibitors were used also showed a high prevalence of physician assisted death in this population.[6] These findings call into question the claim that the risks associated with legalisation will fall most heavily on potentially vulnerable populations.

Are data available about these practices in places where physician assisted death is prohibited? Our study in 1998 assessed the secret practice of assisted death (both physician assisted suicide and voluntary active euthanasia) in the United States, and found significantly higher rates (about one in 50 deaths) than in Oregon after legalisation.[7] The data are not directly comparable, as the study strategy we used safeguarded the surveyed doctors to ensure anonymity (similar techniques are used to study other illegal practices). This may have meant that the participating doctors were less representative and that they reported their practice differently than if the practice were legal. None the less, it raises the possibility that legalisation and regulation with safeguards may protect rather than facilitate the practice.

Are there some cases in legal environments that do not meet the criteria and are not reported? The most controversial cases in the Netherlands are the life ending acts that have no explicit requests (known as LAWER cases – with about 1000 cases each year).[1 2 8] Most, but not all, of these patients were suffering greatly and had lost the ability to make decisions for themselves, and many had previously given consent for physician assisted death under such circumstances. The number of such cases, has decreased over time,[2] but they still account for about 0.4% of deaths that fall outside the Dutch guidelines on voluntariness. It is tempting to attribute such cases to legalisation becoming a slippery slope, but a recent study of six Western European countries—using the same format and questions as the Dutch studies—showed that four of the six countries where assisted death is illegal had a much higher incidence of LAWER cases than is seen in the Netherlands. In fact, such cases were more common than cases of assisted death where voluntary consent was given (either voluntary active euthanasia or physician assisted suicide).[9]

What happens in the US to patients without mental capacity who are dying and whose suffering cannot be relieved by usual palliative measures? Evidence based answers to this question are unknown, but there is likely to be extreme variability in the face of the legal and moral uncertainty about responsibilities, risks, and acceptable approaches.[10] Clinical experience suggests that we deal with many of these patients using terminal sedation,[11] a last resort that has been legal in the US since the 1997 US Supreme Court ruling. No formal tracking is available for this practice in Oregon or elsewhere in the US. Limited data suggest that the practice of terminal sedation is highly variable and accounts for 0-44% of deaths, depending on definitions and programmes.[12] In the Netherlands, terminal sedation accounted for 5.6% of deaths in 2001, compared with 7.1% in 2005 (it was not measured in the first two studies).[2] Many patients who receive terminal sedation are actively dying, experiencing severe physical suffering, and have lost capacity, so some were probably categorised as LAWER cases in previous Dutch studies. Terminal sedation is a legal practice in the US that could be improved if directed by carefully crafted guidelines and reporting.

These days, patients who are dying are faced with a wide array of uncertainties and choices, and the physical and psychological challenges they experience are more complex. Available data suggest the risks and benefits of controversial practices like physician assisted death or terminal sedation are more favourable when practitioners work together with patients and families in an open and accountable environment. Secret practices and arbitrary restrictions should be avoided whenever possible.

Studies such as those by Battin and colleagues from Oregon and the Netherlands help clarify the actual risks and benefits of legalisation of physician assisted death to vulnerable populations. We should ensure that pseudoscientific arguments are not used to promote particular moral values and associated restrictions. Patients who are dying and their families need us to be as objective and honest as possible in these deliberations.

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