Legal threat over off-label drug use

EXCLUSIVE: The drug companies Bayer and Novartis have threatened to take the NHS to court over a new policy to offer patients with wet age related macular degeneration a choice of drugs to treat their condition, including details of price.

Twelve CCGs across northeast England and Cumbria are facing judicial review because they plan to offer bevacizumab (Roche’s Avastin), which is not licensed for wet AMD, alongside ranibizumab (Lucentis, marketed by Novartis) and aflibercept (Eylea, Bayer), which are approved by NICE for treating the condition in the NHS. The CCGs say that the policy will save them up to £13.5m over the next five years.

If hospital trusts in the area agree the plan, patients who receive a new diagnosis of wet AMD will be told that bevacizumab is the preferred choice, because it is as clinically effective as ranibizumab and aflibercept and far cheaper, but that they are free to have one of the NICE approved treatments—in line with English law.

The drug companies maintain that the move breaches a patient’s legal right to a NICE approved drug.

Roche, which markets bevacizumab for various cancers, has never sought a licence for intravitreal use. However, bevacizumab is used off-label around the world, including in parts of Europe and in the US, because it’s far cheaper than the licensed drugs. It has been estimated that in the UK an injection of bevacizumab costs £12.13, compared with £742 for ranibizumab and £816 for aflibercept.

David Hambleton, who is leading the North East and North Cumbria CCG Forum on the issue, said, “As CCGs, we have no interest in protracted legal disputes, but pharmaceutical companies should not dictate which drugs are available to NHS patients. The choice between three clinically effective drugs should be one for NHS clinicians and patients to make together, not for drug companies.”

A spokesperson for Bayer told The BMJ that using “unlicensed medicines” instead of a licensed and NICE approved option “runs the risk of setting a precedent that undermines the regulatory framework and NHS constitution. Bayer feels it has to act to challenge the decision.” Action includes the possibility of legal proceedings.

A spokesperson for Novartis added, “Some information produced by the CCGs about the policy appears misleading and could persuade clinicians and pharmacists (Continued on page 172)
Children waiting too long for mental healthcare

Children and young adults with mental health problems are not receiving the care they need because of long delays and fragmented services, a major review has found.

“It’s been 20 years since the government commissioned its Every Child Matters initiative, and yet so many young people are still waiting too long for the right help at the right time,” said Bernadka Dubicka, chair of the child and adolescent faculty at the Royal College of Psychiatrists, commenting on the review’s findings.

She welcomed the Care Quality Commission’s review of mental health services for young people in England, and said that she hoped it would “result in urgent further investment in child mental health.”

The review analysed 101 reports of recent inspections of specialist mental health services that provide inpatient care or care in the community, along with recent policy and evidence, and it also spoke to the young service users and providers.

CQC inspections rated 26 services (39%) as needing improvement in providing timely access and one service as inadequate. Figures from Public Health England estimated that only a quarter of young people needing mental health treatment were able to access it.

Susan Mayor, London  Cite this as: BMJ 2017;359:j4993

General practice

LMCs will vote on leaving NHS

Local medical committees will debate a motion urging the BMA’s GP committee to support GPs in England to operate privately outside the NHS. The motion, proposed by Bedfordshire LMC, says, “Given that a number of GPs genuinely feel that they can no longer operate within the NHS, conference calls on GPC England to urgently look at how these GPs can be supported to operate within a private, alternative model.” The conference for England’s LMCs takes place in London on 10 November.

Reduced workload “could delay GP retirement”

Less red tape and shorter working hours are the main factors that could persuade older UK doctors to continue working, a study suggested. A paper in BMJ Open analysed responses to a 2014 survey sent to 4 369 doctors who had graduated from UK medical schools from 1974 to 1977. GPs were more likely than peers in other specialties to cite workload pressures as their main reason for retiring.

Mental health

Six standards of care launched in workplaces

Employers are being asked to adopt six core standards to tackle workplace mental health, after an independent review, commissioned by Theresa May, found that 300 000 people with a long term mental health problem lose their job each year. The cost to the economy from workers’ poor mental health is estimated as £74bn–£99bn a year. The six standards include raising awareness, monitoring staff’s mental health, and having plans to help people with problems.

Clinical excellence

Nominations open for 10th BMJ Awards

Doctors have until Friday 26 January to enter themselves or colleagues for The BMJ Awards, now in their 10th year of celebrating outstanding achievement in medicine. The awards span 14 categories: anaesthesia and perioperative medicine; diagnostic; primary care; clinical leadership; outstanding contribution to health; dermatology; palliative and hospice; education; cancer care; innovation; mental health; patient partnership; UK research paper 2018; and emergency. Winners will be announced at a ceremony on Thursday 10 May.

Abortion

MPs back buffer zones at abortion clinics

More than 100 MPs in the Commons backed calls for abortion clinics to have “buffer zones” to protect women from being targeted by anti-abortion protesters. The support was offered in a letter to the home secretary, Amber Rudd, coordinated by Rupa Huq, Labour MP for Ealing, after repeated protests took place outside a clinic in her constituency. Ealing council recently became the first in England to pass a motion to stop anti-abortion groups from protesting outside clinics.

Scotland

Law change permits “abortion pill” at home

Women in Scotland will be the first in the UK to be allowed to take misoprostol—known as the “abortion pill”—at home, when the drug’s licensing is revised. Elsewhere in the UK the drug must be administered in a hospital or licensed clinic. The move brings Scotland into line with countries such as France and Sweden.

Ann Furedi, chief executive of the British Pregnancy Advisory Service, said she hoped that the change would be introduced in the rest of Britain.

Clampdown on junk food promotion

Scotland plans to restrict supermarkets from promoting unhealthy foods in a series of measures to cut obesity. A consultation also proposes introducing a scheme for restaurants and takeaway limits portion sizes and to label calories. Other measures include strengthening current food labelling and restricting billboard advertising of food near schools. The Scottish government also urged the UK parliament to ban broadcast advertising of foods high in fat, sugar, and salt at times when children can view them.

“abortion pill”—at home, when the drug’s licensing is revised. Elsewhere in the UK the drug must be administered in a hospital or licensed clinic. The move brings Scotland into line with countries such as France and Sweden. Ann Furedi, chief executive of the British Pregnancy Advisory Service, said she hoped that the change would be introduced in the rest of Britain.
Prescribing Avoid antibiotics for most sinus infections, says NICE
The National Institute for Health and Care Excellence recommended that most sinus infections do not require antibiotic treatment and that little to no evidence shows that oral decongestants help relieve their symptoms. New NICE guidance, developed with Public Health England, recommends that people with sinusitis should rest and take paracetamol. Most cases of acute sinusitis are caused by a viral infection, and symptoms can last for two to three weeks, it said.

PPIs for acid reflux may increase cancer risk
The long term use of proton pump inhibitors (PPIs) to treat acid reflux is linked to more than double the risk of developing stomach cancer, online research in the journal Gut found. Taking PPIs was linked to more than twice the risk (2.44) of developing gastric cancer, but taking H2 blockers was not linked to any raised risk. The risk increased with PPI dose and duration after elimination of Helicobacter pylori, the study found.

Data security Government was warned of NHS cyberattack
The Department of Health was warned more than once about a likely cyber attack on NHS systems but was unprepared when an attack struck earlier this year, the National Audit Office said. In May, the WannaCry “ransomware” was the largest cyber attack to affect the NHS in England, disrupting at least 34% of NHS trusts and 595 general practices.

Budget Chancellor urged to raise NHS pay cap
Increasing NHS pay in line with inflation could generate an additional £250m of GDP by 2019-20 if the chancellor funds the pay rise in this month’s budget, said a report from the Institute for Public Policy Research. The think tank estimated that raising the pay cap would cost the Treasury less than £1bn by 2019-20, taking into account higher tax receipts, lower welfare payments, and additional GDP generated.

Leaders make urgent plea to fund social care
The NHS Confederation issued an urgent call for extra funds to tackle the crisis in health and care services. A letter to the Treasury ahead of the budget on 22 November warned that the NHS Constitution is being breached and millions of patients face “unacceptable delays” in accessing treatment and support. The letter was signed by medical royal colleges and social services directors. “This is a genuine cry for help,” said Niall Dickson, inauguration chief executive (right).

STUDENTS UK medical schools received almost 20,730 applications in October 2017, up 8% on 2016 when the number was 19,210 (UCAS)

SIXTY SECONDS ON… SEMAGLUTIDE
A drug that treats diabetes and cuts weight? So it seems. A study of 28 obese people in Leeds found that they lost an average of 5 kg and cut food intake by nearly a quarter when treated with semaglutide, an antidiabetes drug being developed by Novo Nordisk.

But that’s a tiny trial There are lots more data. Documents submitted to the US Food and Drug Administration show results from six trials involving almost 10,000 patients. The primary outcome was glycaemic control, but the trials also showed two thirds of participants lost 5% or more of their body weight at the higher dose tested.

So what did the Leeds trial add? It was designed to investigate how semaglutide works. It reduced hunger but also food cravings. These had previously been thought to stem from different parts of the brain, said John Blundell, professor of psychobiology at the University of Leeds, who led the study.

It’s not the first diabetes drug touted as an obesity buster, is it? Indeed not. The old standby metformin often results in weight loss. Other drugs in the same class (the glucagon-like peptide-1 receptor agonists) have shown similar but smaller effects. And then there’s Mediator…

Mediator? The one implicated in France’s biggest drug scandal. It’s believed to have caused at least 500 deaths, and in September prosecutors filed charges of misleading claims and manslaughter against 14 people and 11 organisations, including Servier, which made the drug, and the regulator that approved it.

Not a good precedent Indeed. But the safety profile of semaglutide seems clean, mild gastrointestinal upsets being the commonest side effect. Novo Nordisk wants marketing approval for type 2 diabetes but plans a phase III weight loss trial.

Any downsides? The fact that semaglutide is taken by weekly injection may prove a marketing barrier.

Nigel Hawkes, London
Cite this as: BMJ 2017;359:j5010
Complacency and lack of transparency plague UK research, experts tell MPs

Experts have told MPs that scientific research is suffering from complacency, a lack of transparency, poor statistical skills, and too much weight being given to "exciting" topics. The concerns were raised during an evidence session of the parliamentary science and technology committee's inquiry into research integrity, held on 24 October.

MPs asked witnesses for their opinion on the current state of research integrity, to which Ottoline Leyser, former chair of the steering group on the culture of scientific research at the Nuffield Council on Bioethics, said that a culture had developed "where people are rewarded for being right and being exciting."

Rewards system skewed

She added, "Those things have nothing to do with science and the research method that we want to espouse. These norms of science that everybody would agree to if you pushed them are being not exactly eroded, but counterweighted, by the way that [the] rewards in the research system are currently meted out."

MPs asked the panel whether a "grey area" existed regarding mistakes in research. Dorothy Bishop, professor of developmental neuropsychology at the University of Oxford, also giving evidence, replied, "Some of the [problems] are down to this grey area where people have been told that they shouldn’t do something like p-hacking—"
consultants (up by 3.5% to 45 120), and managers (up by 4.3% to 31 250).

Except for medical workforce numbers, there was no evidence of recent substantial staffing growth in the main professions, while in primary care there were “clear signs of real reductions in the availability of staff.”

Anita Charlesworth, the Health Foundation’s head of research and economics, said, “There is a growing gap between rhetoric about the government’s ambitions to grow the NHS workforce and the reality of falling numbers of nurses and GPs.” She said that instead of a clear strategy to ensure the NHS had the workforce it needed there had been one-off announcements and initiatives, set by “unrealistic timescales.”

She said, “With winter approaching and staffing numbers in critical areas once again declining, the NHS will be relying on the efforts of its staff to meet the inevitable rising pressures. But in the long term both the people working for and the people using the NHS deserve better.”

The Health Foundation said that the NHS in England would be short of qualified nurses by 2021 and that it was unlikely the government would meet its ambition to recruit more GPs from overseas.

Ministers aimed to recruit 2000 GPs from overseas over the next three years, but the report quoted data collected by The BMJ showing that just 38 were appointed in the first six months of 2017.

**Worsening picture**
The Health Foundation said that an annual rate of 30% of staff leaving in some NHS trusts reflected a “worsening picture” of overall workforce stability, “with the likelihood of added costs being incurred at a time when the NHS cannot afford them.”

Danny Mortimer, chief executive of NHS Employers, said, “It’s clear from this important report there is more work to be done in strengthening staff retention and reducing turnover to guard against future instability and protect services to our patients.

“The issue of workforce instability has also been exacerbated by the uncertainty over the future of EU staff working in the health service, and we know it will be necessary to continue recruiting from Europe and elsewhere in the world, as it won’t be possible to fill gaps with increased domestic supply in the immediate term.”

Matthew limb, London
Cite this as: BMJ 2017;359:j5014

**1 PRESCRIBERS**
The prescriptions written by 2873 physicians, nurse practitioners, physician assistants, and other licensed professionals in the district were analysed.

**2 GIFTS RECEIVED**
In 2013 a total of 1 122 (39.1%) of these prescribers received gifts totaling $3.9m ($3m). Individual gifts reported ranged from $7 to $200 000 in cash.

**3 SCRIPTS**
Those who received gifts from drug companies wrote more than twice as many scripts on average as their peers who didn’t report gifts (892 versus 389 prescriptions) in 2013.

**4 BRANDED DRUGS**
Gift recipients wrote more scripts per patient (8.8 versus 6.5) and prescribed more expensive drugs ($135 versus $85), and were more likely to prescribe a branded drug (33.5% versus 25.7%).

**5 DOSE RESPONSE**
People who received more than $500 in gifts were more likely to write more, and more expensive, prescriptions than those who received less.
“Fake psychiatrist” worked in German hospital for a year

A 38 year old man with psychosis and paranoid schizophrenia used forged documents to obtain an assistant doctor post in the psychiatric ward of a German hospital, where he worked for 15 months before the alleged fraud was uncovered.

The documents falsely indicated he had qualified in medicine at Donetsk National University in Ukraine, said the national newspaper Bild. The man, who has not been named, was involved in another alleged fraud a decade ago. In that case, he was accused of forging documents claiming that he was a qualified elderly care nurse. He worked at several care homes from 2006 until the suspected fraud was uncovered in 2011.

In the latest case the man visited the body responsible for checking foreign qualifications in Lower Saxony, north Germany, in early 2016 to have his qualifications certified. He was issued with a temporary licence valid until 2018, and could expect a permanent licence pending the outcome of further investigation, one newspaper report said.

Suspicous documents

The man applied for an assistant doctor position in the psychiatric ward of Ubbo-Emmius Hospital in the city of Norden. He began work at the hospital in March 2016 and remained employed until this June, when the licensing body became suspicious of his documents. The hospital fired the man, but the scandal only surfaced in the press recently.

In 2011 prosecutors—after learning of the alleged nursing fraud—filed charges against the man. But the case was repeatedly postponed as the man underwent treatment for acute psychosis and paranoid schizophrenia. In March 2017, while the man was employed in the psychiatric ward of Ubbo-Emmius Hospital, a district court declared him unfit to stand trial and the case was dismissed.

In the doctor fraud case, German press reports indicated that staff had not suspected him, apparently because he had learnt psychiatric care procedures and language while undergoing treatment for psychosis and schizophrenia.

Thomas Klinge, Hanover’s chief prosecutor, confirmed his office was investigating the man for forgery and fraud.

GMC criticised for investigation into cosmetic surgeon’s case

A cosmetic surgeon accused of improperly anaesthetising a patient and lying to cover it up has been exonerated by a medical practitioners tribunal, which strongly criticised the General Medical Council in bringing the case.

The tribunal also had harsh words for the “fundamentally flawed” original investigation of surgeon Annamalaikani Jeyapragash by Aspen Healthcare, owner of Highgate Private Hospital in north London, where he performed a bilateral breast implant change on “Patient A.” She later complained that she had woken during the procedure despite requesting general anaesthetic.

“Unreliable witnesses”

Numerous witnesses called by the GMC against Jeyapragash were deemed “unreliable,” “evasive,” or not credible, including Patient A, the anaesthetist, the scrub nurse, and the theatre manager, said Nigel Westwood, the tribunal’s chair.

The case dated back to 2012, when Patient A sought a change of breast implants. The operation went without any incident noticed by theatre staff.

But more than a year later the hospital received a complaint alleging that she had woken during the operation, despite expecting general anaesthesia.

The documentary evidence showed that Patient A had consented to sedation and local anaesthetic, the tribunal found. Summing up her evidence, Westwood said Patient A “stated that she did not read documentation, especially documents that included ‘long words,’ including her own letter of complaint.”

Westwood added, “When asked about the consent form she had signed, Patient A stated: ‘It was the normal hospital thing, that you give your permission to blah-blah blah, what-have-you.’”

A theatre manager, who alleged that Jeyapragash had written a false statement and asked her to sign it, proved unwilling to attend and was “obviously reluctant to be examined on her evidence,” said Westwood, dropping the charge.

A GMC spokesperson said, “This has been a very complex case. The tribunal has made a number of comments in its determination, which we will reflect on.”

Locum pay up 6% after tax change

Locum doctors’ average hourly pay has risen by 6% after changes that forced doctors who work through limited companies to pay more tax.

Liaison, a company that manages staff payment systems, gathered data on the locum pay rates and agency commission rates paid by 68 NHS trusts between
Anger at “misleading” redefinition of alcohol deaths

Anti-alcohol campaigners have attacked the Office for National Statistics for redefining deaths related to alcohol use in a way that will reduce the numbers and, they say, mislead the public.

A Lancet Gastroenterology and Hepatology editorial says that the narrower definition adopted by ONS “could come at a steep cost to alcohol advocacy efforts and to the health and well-being of those affected by alcohol misuse and addiction in the UK.”

The effect of the new definition will be to exclude two conditions hitherto included: chronic unspecified hepatitis, which is coded K73 in ICD-10 (international classification of diseases, 10th revision), and fibrosis and cirrhosis of the liver excluding biliary cirrhosis (K74). As a result, instead of recording 6813 alcohol related deaths in 2015, ONS would have recorded 5306, 22% fewer.

ONS put the issue out to consultation in June, offering three choices: the existing definition; the one used by Public Health England (PHE), which excludes conditions only partly attributable to alcohol (including K73 and K74) and includes some wholly attributable conditions not previously included by ONS; and a third option that includes all deaths known to be caused by alcohol and excludes all deaths from conditions that are partly attributable.

The third option gained majority support, ONS said in a report published earlier this month. It will come into force on 7 November. Backers of this option said it would not change the overall public health message, would deal with minor limitations of the ONS and the PHE definitions, and would be closely aligned with international practice.

Harmonising definitions

The Lancet editorial said that harmonising definitions across the UK and with international standards was laudable but adopting the narrower definition was contentious and has been implemented hastily.

The chair of Alcohol Health Alliance, Ian Gilmore, said, “The new definition will mean that a high number of liver disease deaths where we know that alcohol is the cause will no longer be recorded as being linked to alcohol.

“This reduction will give the wrong impression to the public that alcohol deaths are going down, when in fact the burden of alcohol on our nation’s health and health service is growing, with alcohol related hospital admissions going up and liver disease rates on the rise.”

As a result, instead of recording 6813 alcohol related deaths in 2015, ONS would have recorded 5306 alcohol specific deaths, 22% fewer.

April and June 2017. The company found that the average hourly pay for locums increased by 6.3%, from £66.26 in the last quarter (January to March) of 2016-17 to £70.41 in the first quarter (April to June) of 2017-18.

Biggest increase

Over this period the average hourly pay rates for locum consultants, year 3 specialty trainees (ST3s), year 2 foundation trainees (F2s), and staff grade doctors all increased. The biggest increase was in pay for ST3s, whose hourly rate increased by £3.73, from £61.51 in the last quarter of 2016-17 to £65.24 in the first quarter of 2017-18.

The data also showed that locums continued to be paid more than the capped rate set by NHS Improvement. In November 2015 a cap on the hourly rate that NHS trusts could pay locums was introduced.

Trusts can hire staff at rates above the cap when there is a legitimate patient safety requirement, but they must get their chief executive to sign off all total hourly rates that exceed £120 an hour. Any breaches of the £120 cap must be reported to NHS Improvement.

In the first quarter of 2017-18, 7% of locums were paid in excess of £120 per hour, Liaison found, up from 5% in the final quarter of 2016-17. If the top 10 highest earning locums in the first quarter had had their pay limited to the cap, the annual saving to the NHS would be £789 000, Liaison said.

Abi Rimmer, The BMJ

Cite this as: BMJ 2017;359:j4939
To celebrate 50 years of providing free advice to the public and professionals on issues related to drug use and drug law, the charity Release is hosting the Museum of Drug Policy exhibition in south London.

The pop-up cultural hub, which has been hosted in New York and Montreal, features live programming and art from around the world, highlighting how drug policies shape communities. It aims to illustrate the harms caused by drug prohibition, and advocates for new approaches rooted in dignity, health, and human rights. The museum, supported by the Open Society Foundations, was installed at the Ugly Duck art space in Southwark and will run until Sunday 5 November.

The exhibition features artwork from around the world including Progress? (right) by Michael D’Antuono, which questions how far black Americans have come since slavery; and ...And Counting (above left), by the artist GILF!, an installation of toe tags representing people killed by the police.

Alison Shepherd, The BMJ  Cite this as: BMJ 2017;359:j5041
The future of QOF in England

It’s time to rethink one of the most ambitious experiments in general practice

To describe the Quality and Outcomes Framework (QOF)—one of the most ambitious pay-for-performance schemes introduced into any health system—as divisive would be an understatement. Launched in the UK in 2004 as a way of encouraging adherence to specified evidence based elements of general practice care, QOF has changed the nature of general practice in ways that have polarised those who work in the sector and external commentators.1

Advocates highlight how patient care, especially for those with long term conditions, is now more structured, more systematic, and more likely to be based on high quality research evidence. Others have expressed concerns about both the intended and the unintended consequences of QOF. Critics claim that using financial incentives to focus attention on aspects of care that are easily measured has diverted attention from interpersonal elements that are less easily objectified.

Has QOF worked?
Although many changes have been made to structures and working processes, a big question is whether QOF has improved outcomes for patients. The evidence is far from convincing. Observational studies suggest modest improvements in some aspects of clinical care,2,3 a small reduction in the rate of increase of emergency admissions for incentivised conditions,4 but no clear effect on overall mortality.5 There is little empirical evidence that QOF has a negative impact on the coordination or integration of care, the provision of holistic care, or patient experience, but little sign of benefit either.6 These findings are consistent with evidence from other parts of the world, that financial incentives are often less effective than those who bring them in expect.7

QOF has become increasingly unpopular with GPs, partly because of the administrative demands of the scheme at a time of rising workload, and partly because of indicators introduced in the past few years that were poorly evidence based or seemed to tackle a managerial rather than a clinical agenda. Inevitably, questions are being asked about its future. In 2015, the Royal College of General Practitioners (RCGP) called for it to be replaced by a system of payment that encouraged a more holistic approach to patient care.8 In 2016 QOF was abolished in Scotland and replaced by a requirement for GPs to take part in local peer led quality improvement activities (GP Quality Clusters).9 Some localities in England have replaced QOF with local incentive schemes, and earlier this year NHS England said that it was committed, in principle, to removing QOF altogether.10 The BMA, however, has called for it to be retained, in part because of the likely disruption and the risk to practice income if it were abolished.11

Opportunity for the future
QOF should be changed only if whatever replaces it is better for patients, for individual practices, and for the sustainability of general practice as a specialty. There are a number of principles that should guide any replacement. First, there may be a case for retaining a limited number of indicators with clear relationships to health outcome—or at least measuring these to ensure that quality does not decline when incentives are removed. Second, whatever replaces QOF must build on the professionalism and goodwill that still exist in general practice: Scotland has made a bold statement of confidence in the profession, and England could be equally courageous.

Third, in line with the recently published RCGP position statement on quality,12 new arrangements should place a greater emphasis on encouraging a process of continuous improvement in care rather than the attainment of standards. A focus on these last two will recognise the value of the more complex activities that general practice must pursue, such as managing uncertainty, engaging with the social determinants of health, and encouraging shared decision making with patients.

Fifteen years ago we asked whether QOF would be the renaissance or the requiem for general practice.13 It has been neither. Most commentators agree that it has resulted in some benefits and caused some harm. Policy makers and the profession now have an opportunity to move on and do better.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.j4681
Men’s reproductive health and the environment

Disturbing trends demand urgent attention

A recent meta-analysis by Levine and colleagues showing significant declines in sperm counts among men in the Western world caught considerable media attention.1 The Levine study followed a similar report in The BMJ 25 years ago.2 Should we be concerned? Is male reproductive health really at risk? Meta-analyses have some inherent limitations. However, an important and often overlooked point about data on the quality of semen is that trend data should be interpreted with a holistic view of male reproductive health problems, including parallel trends in testicular germ cell cancer (TGCC). Incidence of this cancer has risen substantially over the past few decades, particularly in young men.3 Increases seem to be occurring even in countries that have had low incidence. TGCC is linked to risk of poor semen quality: reports suggest that countries with a high incidence of this cancer have generally lower semen quality and vice versa.4

Another good reason to pay special attention to the trends in testicular cancer is that registry data are considered to reflect true disease incidence. There are no large screening programmes that might skew incidence rates, as there are with cancers such as prostate. Importantly, strong clinical evidence exists that testicular cancer and spermatogenic disorders are biologically inter-related.5 This relation seems to have a fetal origin—congenital cryptorchidism is a risk factor for both TGCC and poor semen quality.6 One hypothesis is that these male reproductive disorders may be linked through a testicular dysgenesis syndrome,7 also affecting the function of testosterone producing Leydig cells. The serum testosterone concentrations among healthy men in the US, Denmark, and Finland have shown noteworthy falls over recent decades.8

Environmental influences

What could be causing such disturbing trends? The short answer is that we do not know. However, data suggesting that the incidence of testicular cancer has more than doubled in recent decades' leave little doubt that we should look into environmental causes—including lifestyle effects. Alterations in our genome cannot explain the observations as changes have occurred over just a couple of generations.

Environmental exposures can come through food, water, skin, and work and home environments. Both wildlife research and experimental studies suggest that modern lifestyles are associated with increased exposure to various endocrine disrupting chemicals such as pesticides that together may be harmful to wildlife and humans even though exposure to individual chemicals is low.9,10,11 However, little has been done to explore their potential effects on semen quality and testicular cancer. In particular, studies of maternal exposures in pregnancy and the subsequent reproductive function of their sons are needed.

Should we be worried about our future ability to reproduce ourselves, as some media coverage has claimed?12 This inconvenient question makes sense when we look at what is going on in fertility clinics all over the world—more and more children are now born after in vitro fertilisation, intracytoplasmic sperm injection, and insemination with partner or donor sperm.13 However, despite increased use of assisted reproduction, fertility rates in many countries remain well below the replacement rate of an average of 2.1 children per woman. In many European countries, including Germany, Japan, and Singapore, fertility rates range between 1.0 and 1.5, and fertility has become important in political and economic debates.

In order to help future generations we must act now to prioritise new basic and clinical research programmes in reproductive medicine. Simple research questions urgently need answers.

Medical researchers cannot do it alone. We need health and research authorities that can see the urgent need for research in reproductive medicine, not just more infertility treatments, which are a short term solution for individuals not for the fertility of future generations.

We have already waited too long. As New York Times columnist Nicholas Kristof recently wrote: “Our human future will only be as healthy as our sperm.”14,15

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INVESTIGATION

Cutting the ties that bind doctors to pharma in fight for cheaper eye treatments

A plan to prescribe bevacizumab for macular degeneration despite legal threats from drug companies, and against GMC and NICE guidance, hints at a turning point in a long running battle in which £500m potential NHS savings are at stake. Deborah Cohen reports

The tide may be turning in the story of bevacizumab (Avastin) as a treatment for wet age related macular degeneration (AMD). In response to The BMJ’s revelation that doctors in the north east of England face legal action over their new policy to offer patients that option (see This Week, p 169), commissioning leaders have thrown their weight behind them—and the doctors’ regulator seems to be softening its stance against such moves.

What is at stake, say the doctors involved in the latest battle, is the principle that the choice between clinically eff ective and safe drugs should be one for clinicians and patients, not drug companies. They estimate that prescribing bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), could save the NHS millions of pounds in their 12 clinical commissioning group (CCG) areas every year (see commentary, p 182). Across England, those savings could total more than £500m a year if used for all relevant eye conditions.

In addition, the latest chapter in this story calls into question the influence of the government on guidance from NICE.

### Potential savings

Two anti-VEGF drugs are approved to treat wet AMD on the NHS: ranibizumab (Lucentis), marketed by Novartis in Europe, and aflibercept (Eylea), produced by Bayer. Roche (which developed Lucentis and retains the commercial rights in the US) markets bevacizumab for use in various cancers—some of which lack evidence of clinically meaningful benefit—but has never licensed it for use in the eye. This is despite meta-analysis of several publicly funded clinical trials finding that bevacizumab is as safe and effective as ranibizumab for wet AMD.

Bevacizumab is also far cheaper. In 2015 a group of ophthalmologists found, through freedom of information requests, that NHS eye units had given more than 50,000 injections of anti-VEGFs—including 14,100 of bevacizumab—costing the NHS an estimated £45m in a single month. Some of the injections were for other indications such as diabetic macular oedema, for which there is also some evidence that bevacizumab is eff ective.

They calculated that if bevacizumab was used for all injections instead of ranibizumab or aflibercept, the estimated cost would be £729,500 a year, saving the NHS an estimated £539m a year.

The new policy from the North East and North Cumbria CCG Forum aims to realise some of these savings by offering patients a choice. Clinicians will tell patients newly diagnosed with wet AMD that bevacizumab is the preferred choice but that they are free to choose one of the NICE approved treatments—ranibizumab and aflibercept—in line with English law. Bayer and Novartis say that the policy breaches patients’ legal right to a NICE approved drug, and are seeking a judicial review.

Bevacizumab is routinely used in private practice, according to Andrew
Lottery, professor of ophthalmology at Southampton University. “Many insurance companies don’t pay for chronic conditions such as age-related macular degeneration,” he says. “Patients have to pay out of pocket for bevacizumab, which is far cheaper than the licensed drugs.”

The CCGs are backed by their representative organisation NHS Clinical Commissioners. Its chief executive, Julie Wood, tells The BMJ: “We support our members in doing all they can within the law to deliver the greatest value for the commissioning pound while getting the best outcomes for patients. Using bevacizumab off-label to treat wet AMD is an opportunity for them to do just that.”

**Off-label prescribing**

However, doctors prescribing bevacizumab for wet AMD on the NHS will be going against the GMC’s guidance on prescribing and managing medicines, which discourages use of off-label or “unlicensed” products when there is a licensed alternative.

Ophthalmologists say that the GMC guidance has deterred them from prescribing bevacizumab despite the evidence of its efficacy and safety, and the financial strain on the NHS. The Royal College of Ophthalmologists cannot take a position that flies in the face of the doctors’ regulator, says Lottery, who chairs the college’s scientific committee and was an investigator on the UK publicly funded IVAN trial that compared bevacizumab with ranibizumab for wet AMD. “It’s purely the regulatory framework that is stopping bevacizumab’s widespread use in the NHS,” he says.

Back in 2015, The BMJ questioned the interpretation of European law that led to the GMC’s stance.1 The advice seemed at odds with practice in other European countries.

In the Netherlands, as well as being used for wet AMD, bevacizumab had become standard treatment for diabetic macular oedema—the most common eye condition treated with anti-VEGFs—on the basis of cost.2 A Guernsey eye service (which Lottery provided) also used only bevacizumab in 2015.3 The GMC has confirmed that doctors practising there are registered with it. No fitness to practise case has ever been brought because a doctor was using bevacizumab for ocular conditions rather than a drug licensed for that purpose.

Despite this, Niall Dickson, then chief executive of the GMC, told The BMJ that doctors in the UK couldn’t use intravitreal bevacizumab for legal reasons. “The main problem is the law,” he said, adding later that it was unequivocal and pointing to a 2012 European Commission case against the Polish government to support the GMC’s view.

The court found against Poland because it was importing unlicensed drugs for economic reasons when licensed ones were available. “The European Court of Justice (ECJ) has in effect ruled out the adoption of blanket policies that permit the off-label/unlicensed prescribing of medicines on the grounds of cost,” said Dickson.4 The BMJ queried the relevance of this case and asked the GMC for a copy of the legal opinion that resulted in the guidance, but the regulator refused. A spokesperson said it attracted “legal professional privilege” and the public interest was best maintained by not releasing it.

Public health consultant Greg Fell pointed out at the time: “Without this, it is impossible to judge the validity of the GMC’s line.”

And the validity of the GMC’s line is in question. If shown to be wrong, it has potential to cost the NHS hundreds of millions—if not billions—of pounds and distorted clinical priorities.

**Shifting legal position**

At the end of September, an official adviser to the European Court of Justice (ECJ) gave his opinion on a case referred by Roche and Novartis, who were seeking to overturn a 2014 ruling by Italy’s competition authority.

The ruling led to the companies being fined €180m for allegedly colluding to prevent the use of bevacizumab, by exaggerating the risks of using it to treat wet AMD and portraying ranibizumab as safer. Italy’s health ministry had also announced that it would seek damages of €1.2bn in 2014.

Henrik Saugmandsgaard Øe, an ECJ advocate general, took the view that off-label drugs can be considered in place of licensed drugs for various reasons, including their price.5 If the advocate general’s opinion is upheld by the ECJ—and it usually is—it will be “potentially helpful in tackling some of the legal challenges” to the north east CCGs, Wood says.

A spokesperson for Roche told The BMJ that it doesn’t comment on ongoing legal action. In a statement, Novartis said: “Some information produced by the CCGs about the policy appears misleading and could persuade clinicians and pharmacists to act in accordance with the policy, even if such practice might be in breach of their respective professional obligations.”

Faced with the ECJ opinion, the GMC is less strident than two years ago on commissioning policies, saying that it is “sympathetic to the frustrations of doctors and organisations seeking to use resources effectively.”

“We understand there may be current legal cases that could clarify the position on commissioning and prescribing decisions around certain unlicensed drugs, and are keeping a close watch on how this might develop,” Mary Agnew, the assistant director of standards and ethics, tells The BMJ.

“We hope some sort of licensing solution for drugs such as Avastin may be forthcoming,” says Agnew, “but we will have to be flexible.”

**Back in two trillion one,” he says.**

**The BMJ** approached the UK Medicines and Health Care Products Regulatory Agency (MHRA) for comment, but its spokesperson said “it would be premature for it to comment before a final decision has been reached.”

A spokesperson for Bayer told The BMJ that bevacizumab needs to be “compounded into syringes creating a different and unlicensed medicine.”

Using “unlicensed medicines” instead of a licensed NICE approved option “runs the risk of setting a precedent that undermines the regulatory framework and NHS constitution.”

“Bayer feels it has to act to challenge
the decision taken by these CCGs,” the spokesperson said, which includes the possibility of legal proceedings. “We are determined to work with the appropriate authorities to ensure a resolution that is lawful and protects the interests and wellbeing of patients.”

The CCGs, however, are questioning whether intravitreal use of bevacizumab, which needs to be split into vials, is indeed unlicensed. In 2015, the European Medicines Agency dismissed the notion that bevacizumab was an unlicensed product when used in this way. It stated that the use was “off-label.” The US Food and Drug Administration agreed.9

**NICE guidance**

The ECJ opinion could also affect NICE’s draft guideline for the treatment of macular degeneration.10 When NICE was instructed by the Department of Health in 2014 to produce the guideline, it knew it was controversial.

Sources have told *The BMJ* that the institute was prepared to fight its corner; it was willing to recommend the most cost effective drug based on the evidence, irrespective of the licensing situation. This would have given doctors a firm rationale for their decision if they opted to use bevacizumab over a licensed drug because of cost effectiveness and, as a result, ended up in court or in front of the GMC.

But NICE backtracked. *The BMJ* has learnt that, behind the scenes, senior governmental health officials have suggested that NHS decision makers need to be mindful of the needs of the drug industry, particularly in light of Brexit.

While the draft NICE guidelines state that bevacizumab provides the best value for money for treating macular degeneration, it cautions that GMC guidance should be considered if prescribing outside a licensed indication. Cost should not be taken into account. It adds that bevacizumab can be prescribed for AMD only if a “person has a specific need and no other licensed product meets that need.”

When *The BMJ* asked NICE about the inclusion of this clause in light of the ECJ opinion it batted the decision back to the GMC. “Our guidance, in respect of the off-label/unlicensed use of medicines, reflects the rules imposed by the GMC. As such we will continue to reference the GMC in our guidance,” a spokesperson said.

In the private sector, however, an individual’s need may include cost. In the NHS, the cost need is transferred onto someone else—a person potentially losing out on a treatment because the money has been spent on a more expensive drug.

The NHS desperately needs the £500m that the unearthing of these various legal knots—and therefore the prescribing of bevacizumab for wet AMD—could save, not least in eye services themselves, says Lotery. His eye unit at University Hospital Southampton is experiencing “extreme pressure” because of lack of capacity—as are other hospital eye services across the country, he says.

“Savings made by using bevacizumab should be reinvested into the hospital eye service to build capacity to deliver sight saving treatment for age related macular degeneration.”

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**COMMENTARY David Hambleton**

**NHS patients should have a choice of drug for wet age related macular degeneration, despite pharma pressure**

Commissioners have to pay more than lip service to the obligation on us to find cost effective treatment options. Our 12 clinical commissioning groups (CCGs) have therefore agreed a policy to offer the thousands of patients in our region diagnosed with wet age related macular degeneration (AMD) every year the choice of bevacizumab as preferred treatment.

That bevacizumab is as clinically effective and safe as aflibercept and ranibizumab—which patients will continue to be offered as alternatives—has been shown comprehensively. We intend to share information with patients through accessible media (including leaflets and audiovisual material) about the treatment options available, the evidence base, and the comparative costs—and allow them to make their own choice.

The policy could save the region’s NHS up to £13.5m a year over the next five years. That could pay for an extra 270 nurses or 266 heart transplants every year. In a financially stretched NHS, the alternative for CCGs is to be treated with aflibercept or ranibizumab that is the drug the NHS will provide.

Every patient who chooses the cheaper alternative drug will help the NHS to fund important medical treatment in other areas. We want to have informed conversations with our patients so that they understand the wider effects of the choices we collectively make. If a patient chooses to be treated with aflibercept or ranibizumab then that is the drug the NHS will provide.

As CCGs, we have no interest in legal disputes, but drug companies should not dictate which treatments are available to patients. The choice between three clinically effective drugs should be one for NHS clinicians and patients to make together.

We are confident that EU drug marketing laws do not allow drug companies to restrict the ability of the NHS to offer patients a choice. Our legal position is strongly supported by official advice to the European Court of Justice handed down in September.1 That is why we have responded robustly to Bayer and Novartis, which have threatened a judicial review in an attempt to deny NHS patients this choice.2

The companies frequently refer to “unlicensed” use of bevacizumab, which seems to imply that it is unsafe. This is clearly not the case, either in law or in practice, where licensed drugs are safely and effectively used off-label on a daily basis in the NHS.

We understand that there may be some confusion among clinicians about this issue, and we will offer every support to ensure they can have confidence in their clinical right to prescribe what is best for the patient, while being mindful of their duty to consider the best use of NHS resources.3 The CCGs have taken legal advice and we are confident that we are acting lawfully—in the same way that clinicians prescribing bevacizumab to private patients with wet AMD are acting lawfully.

Clinical safety and effectiveness are paramount but, as the legal guardians of finite NHS resources, we commissioners also have a duty to act efficiently, effectively, and economically. Difficult choices have to be made to ensure safety and sustainability—this is one choice that is morally and ethically palatable.

David Hambleton chief officer, South Tyneside Clinical Commissioning Group, Jarrow

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last month, what might be termed a “cancer drugs scandal” hit the headlines. The trigger was a package of BMJ articles laying bare that the approval of most cancer drugs by the European Medicines Agency was based on “flimsy or untested surrogate outcomes.” To the limited extent that the impact of these drugs has been studied over time, they seldom appear to deliver “clinically meaningful benefit.” A Mail Online headline was blunt: “The costly cancer drugs that don’t help patients.”

A second worrying message, not picked up by newspapers, came from an oncologist in a response to The BMJ’s articles: that “production line systems adopted by the NHS...encourage doling out of chemotherapy without thought.”

Oncologists argue that patient pressure is what makes them prescribe—an apologia I don’t find wholly convincing

As a patient and patient advocate I repeatedly hear, read, and observe stories of bravery, disillusion, and despair. Many patients and carers, including me, are deeply traumatised by their cancer journey. Fellow travellers describe the shock of diagnosis, the fear, and then often a determination to “beat cancer” by taking unpronounceable drugs and other treatments. Next comes the exhausting struggle to “comply” with complex regimens, access disjointed and often distant services, and cope with distressing and debilitating side effects. Finally, are the progressive loss of morale and hope, the inexorable erosion of quality of life, and the realisation that treatment will not deliver on its promise.

The options are seldom easy, of course, and no one forces patients to embark on chemotherapy, aggressive or otherwise. Indeed, oncologists argue that patient pressure is what makes them prescribe—an apologia I don’t find wholly convincing. Patients may be desperate for “magic bullets,” but they take doctors’ advice seriously. It’s a professional responsibility to present uncomfortable truths, to be transparent about evidence limitation and how treatment “effectiveness” is judged, and to be objective about risks, harms, and benefits.

Undeniably, many new cancer treatments are highly effective, and the issue for patients is accessing them. New research and personalised medicine have opened up exciting avenues. But we live in the present, and what seems a near universal message is that treatment discussions are often woefully inadequate.

BIOGRAPHY

Dr Tessa Richards (above) is a senior editor at The BMJ and leads the journal’s patient partnership initiative. Her professional interest has been advanced by her experience as a carer for close family members with rheumatoid arthritis, dementia, and blindness. Tessa herself was diagnosed as having adrenal cancer in 2004 and underwent thoraco-abdominal surgery followed by further surgery to remove metastases.
Patients may get their diagnosis, prognosis, and proposed treatment laid out in a couple of short outpatient sessions. Although this may be deemed efficient, a recent report from the charity Macmillan Cancer Support suggests that about a quarter of people with a cancer diagnosis don’t fully understand what’s wrong with them and that half are not fully informed about side effects. In an eloquent response, Ceinwen Giles, a member of The BMJ’s patient panel, has underlined how getting a diagnosis is “numbing” and how patients need time to formulate the questions they need answering.

**A production line affair**
Shortage of time is a big problem, but it’s not the only one. Decision making in oncology has evolved into a production line affair. Patients packaged as “cases” are processed through multidisciplinary teams. The focus is on scan and test results and treatment options. Consensus on “recommended” treatment may be reached with little or no reference to patients’ goals, hopes, fears, or preferences. The voice of upbeat interventionists tends to trump others and can fuel more aggressive treatment.

When a panel of experts has come to a decision it’s hard even to question it, let alone row back on it. I’ve tried this and found that it doesn’t endeavour you to your clinicians. Nor does asking to attend the multidisciplinary meetings, to get an understanding of the rationale for decisions. A recent request I made was met with surprise and a sharp, “No, we are not set up to include patients.” When I declined chemotherapy that was recommended by a consultant I’d never met (on the basis of a discussion about my case that I didn’t know was taking place), his conclusion, incorrectly, was that I lacked the will to live.

As a doctor I know about practice variation and why expert views may differ, but it’s bewildering when you encounter it as a patient. When I presented with a fourth recurrence of my adrenal cancer in the caudate lobe of the liver 18 months ago, various lines of treatment were suggested by the consultants I saw. They included immediate surgery (deemed very risky): adjuvant chemotherapy, with a view to shrinking the tumour a bit prior to surgery; joining a phase I clinical trial (I was advised to “chase this option fast” but weeks later was told that I wasn’t eligible); undergoing a second course of abdominal radiotherapy (my first was more than 10 years ago); and taking a long used, but notoriously hard to tolerate, “holding” drug for adrenal cancer, called mitotane.

Evidence on the likely outcomes of these options was not clear. I struggled to make a decision and, while I did so, I discovered other possibilities through independently supported “crowdsourcing.” These included new forms of endoradiotherapy and percutaneous NanoKnife ablation. (I plumped for radiotherapy and, when this failed to shrink the tumour, underwent NanoKnife treatment privately, to good effect.)

**Mutually well informed and fully shared decisions**
The option to do nothing was not proffered, although I wanted to explore it. I knew that I couldn’t face major surgery again and was opposed to taking toxic drugs that were unlikely to confer benefit and guaranteed to undermine my quality of life. So, I summoned the courage to ask the oncologists about the likely endgame. About a year, they said, looking rather uncomfortable—with jaundice and ascites or with severe pain associated with invasion of the coeliac plexus before death. I mulled things over and, on the advice of a trusted medical friend, went to the GP to ask for referral for an early discussion about palliative care. She seemed flummoxed. “I don’t know the palliative care doctors,” she said. “You could maybe get in touch with them at the hospice yourself. We refer people at the end of life.”

**HEALTHCARE’S WICKED PROBLEMS**
Sometimes insight into healthcare is an advantage; sometimes not. When I’m below par or awake at night I sometimes relive stressful hospital episodes and churn over healthcare’s wicked problems in relation to my journey. When I’m well, as I largely am now, I park apprehension. Knowing that your time’s limited is a great spur to “seize the day.” For me this includes advocacy for established movements and campaigns, which are integral to the wide responses we need to the “cancer drugs scandal.”

Better approval and oversight of cancer drugs is a clarion call. But so too should be the call for mutually well informed and fully shared decisions. The quality of decision making will improve when we resolve the power imbalance regarding access to information. The case for integrated records is well accepted, but the case for giving patients full, real time access to their records and test results, as well as control over the use of their health data, is still a logistical and ideological battle in progress despite accumulating evidence of benefit.

I also support the right to a second opinion. Patients surely have the right to question doctors, explore options, and have views on “best” treatment. Those who do their research, and who seek the wisdom in networked patient communities, should not be branded overdemanding or difficult.