# this week

**NHS'S MONEY WOES** page 172 • **EXERCISE FOR SEDENTARY WORKERS** page 170


# Trust backs doctors' private clinic

Two consultants who started a private clinic that then took on overflow work from the NHS trust that employed them did not do anything wrong, the trust has said.

Steve Pandey, clinical director of colorectal surgery, and Stephen Lake, clinical director of endoscopy, from Worcestershire Acute Hospitals NHS Trust, registered the private Worcestershire Bowel Clinic in January 2012. The two consultants are directors of the clinic, which is based at the private Spire South Bank Hospital in Worcester. The clinic was subsequently contracted by the trust to treat NHS patients with bowel cancer through waiting list initiatives.

However, last week the two doctors found themselves at the centre of an exposé by the *Birmingham Mail*, which revealed details of the arrangements under the headline, "Trust spent £1m treating NHS patients at private clinic run by its own consultants."

In a statement the trust said, "There is categorically no evidence of any wrongdoing on the part of the consultants in question." The trust said that it would launch an investigation "into the arrangements for consultation on service change and the process followed for participants to declare and record their interests outside of the trust." It emphasised that, contrary to media reports, "this is not an inquiry into the actions of the consultants concerned."

The article said that none of the work that went to the Worcestershire Bowel Clinic was put out to tender and that neither consultant made an official conflict of interest declaration until 2015.

The trust pointed out, however, that the endoscopy contract was awarded under "Any Willing Provider" rules, for which no tendering was required, and the Worcestershire Bowel Clinic was the only provider in close proximity to come forward.

Pandey and Lake formally declared their links to the Worcestershire Bowel Clinic in 2015. It was unclear whether formal written declarations were made before this, but informally managers and other staff at the trust were aware of the connection.

Chris Tidman, chief executive of Worcestershire Acute Hospitals Trust, "We have not been able to trace any formal declaration of interest from either of the consultants prior to [2015], but this doesn't necessarily indicate any wrongdoing."

Ingrid Torjesen, London

Cite this as: *BMJ* 2016;354:i4157

**Stephen Lake (left) and Steve Pandey (right) are directors of the Worcestershire Bowel Clinic which opened at the the private Spire South Bank Hospital in Worcester in October 2013**

## LATEST ONLINE

- Range of generics will be withdrawn across Europe
- Former Johnson & Johnson executives are convicted over off label marketing
- US probes first apparent non-sexual person to person Zika transmission

# SEVEN DAYS IN

## An hour's exercise offsets impact of sitting all day

**Doing at least an hour a day of moderate physical activity, such as brisk walking or cycling, seems to eliminate the increased risk of death associated with sitting for more than eight hours a day, a study published in the *Lancet* shows.**

**The analysis included data from 16 studies on 1 005 791 people who were followed up for 2-18.1 years, during which time 84 609 (8.4%) died. People who did the least physical activity had a 12-59% higher risk of death during the follow-up period than those who sat for less than four hours and did 60-75 minutes of moderate activity a day. The hazard ratio of the enhanced death rate ranged from 1.12 (95% confidence interval 1.08 to 1.16) in people who did 25-30 minutes' moderate activity a day and sat for less than four hours, to 1.59 (1.52 to 1.66) in those who did about five minutes' moderate intensity activity a day and sat for more than eight hours.**

**Prolonged sitting was also shown to increase the risk of death, but the effect was mitigated in the most active people. People who did 60-75 minutes' moderate activity a day showed little effect from sitting for more than eight hours when compared with less than four hours (1.04 (0.99 to 1.10)). However, sitting for more than eight hours rather than four increased the risk of death in those who did the least amount of moderate activity (around five minutes a day) by around a quarter (1.27 (1.22 to 1.31)).**

Ingrid Torjesen, London Cite this as: *BMJ* 2016;354:i4166

## Public health

**Vitamin D is urged in autumn and winter**

Children and adults should take a daily supplement containing 10 µg of vitamin D in autumn and winter to protect bone and muscle health, as it is difficult to meet this intake from dietary sources, Public Health England recommended. Evidence showed that vitamin D supplementation improved bone health in adults over 50 and bone health indices in newborns whose mothers took the supplement while pregnant. (Full story doi:10.1136/bmj.i4061)

**Nearly 6000 cases of FGM were identified last year**

Some 5700 new cases of female genital mutilation (FGM) were recorded in 2015-16 in the UK, 18 of which were performed here, the first annual statistics from the Health and Social Care Information Centre showed. FGM was most common in girls aged 5 to 9 (43%), and more than one third (37%) of the girls were born in Somalia.

## General practice

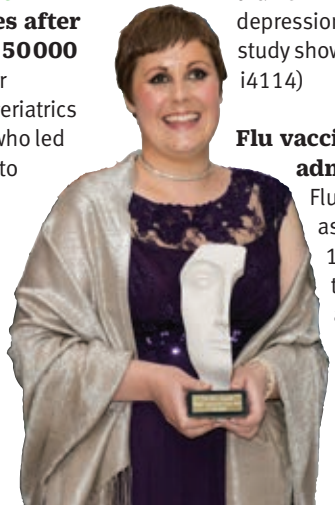
**Patients will wait a week for GP by 2020**

Patients will have to wait more than a week to see a GP on 100 million occasions by 2020-21, an analysis by the Royal College of General Practitioners showed. This compares with 69 million times in 2015-16. Demand for appointments will be so high in 2020-21 that 52 million patients will be unable to get one. In 2015-16, 9.4 million were unable to secure a GP appointment and had to seek healthcare elsewhere.

## Patient care campaigner is mourned

**Doctor dies after raising £250 000**

Kate Granger (right), the geriatrics consultant who led a campaign to encourage NHS staff to introduce themselves properly to patients and who published diaries of her experience with cancer, has died aged 34. Granger raised more than £250 000 for the Yorkshire Cancer Centre from sales of her two books about having cancer. She won a Special Achievement award at The BMJ Awards in May. (Obituary, p 194)



## Research news

**Simpler treatment may be as good as CBT**

Behavioural activation, a simpler type of psychological treatment than cognitive behavioural therapy (CBT) that helps people focus on changing how they act rather than how they think, is as effective as and cheaper than CBT in treating adults with depression, a large randomised study showed. (10.1136/bmj.i4114)

**Flu vaccine reduces admissions**

Flu vaccination was associated with a 19% reduction in the rate of hospital admissions for acute myocardial infarction, a 30% reduction in admissions for stroke, a 22% reduction in admissions for heart failure, and a 15% reduction in admissions for pneumonia or flu, a study has found. It involved 124 503 adults from 300 general practices in England. (10.1136/bmj.i4130)

## Medical workforce

**Call for action to keep older doctors in work**

The Association of Anaesthetists of Great Britain and Ireland urged a review of the demands on older doctors so that their working patterns can be adapted to allow them to keep working safely. Doctors must work until 67 to claim a full NHS pension, but many retire earlier, leaving gaps in rotas, which are predicted to worsen. Job and career plans for anaesthetists must reflect their capacity to adapt to night work and their mental and physical strengths, the association said.

# MEDICINE

Festival goers in the UK had the opportunity to have their drugs tested for the first time in July; a quarter then ditched them

**Surgeon is suspended for altering notes**

Jose Mullerat, a consultant surgeon, was suspended for four months after a fitness to practise tribunal found that he had retrospectively added a line to a patient's notes after her death and claimed that it was contemporaneous. Lyn O'Reilly, 57, of Tilbury, Essex, died of peritonitis from a burst abscess a week after gastrointestinal surgery. Mullerat added a line to her notes after learning of her death. (10.1136/bmj.i4059)

## Screening

**Evidence on skin cancer screening is lacking**

Evidence is insufficient to determine whether early detection of skin cancer, including melanoma, through routine visual skin examination by a clinician reduced morbidity or mortality, the US Preventive Services Task Force concluded in *JAMA*. The task force gave its recommendation an "I" designation, indicating insufficient evidence to make an assessment. The evidence was adequate, however, to conclude that the risks of such examinations are small. (10.1136/bmj.i4155)

## Illicit drugs

**UK festival goers get their drugs tested**

Music fans attending the Secret Garden Party in Cambridgeshire from 21 to 24 July were able to have their illegal drugs tested to find out exactly what they were taking, for the first time ever in the UK. Around 200 people made use of the police backed scheme, run by a community interest company, The Loop. Concerns were raised over around 80 samples, including ketamine cut with malaria tablets and ammonium sulphate sold as MDMA. Around a quarter of people asked for their drugs to be disposed of after they were analysed.

## Clinical trials

**European rules for trials to be tightened**

The European Medicines Agency (EMA) proposed changes to its current guidance on first-in-human clinical trials, to reduce risks to participants. The changes were outlined in a concept paper and follow lessons learnt from the phase I first-in-human clinical trial of Bial's FAAH anxiety drug BIA 10-2474. In the January 2016 trial in Rennes, France, one patient died and five were seriously ill.

Cite this as: *BMJ* 2016;354:i4148

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The number of antidepressants prescribed and dispensed in England rose from **57.1m** items in 2014 to **61m** in 2015, the biggest rise of any drug (HSCIC)

# SIXTY SECONDS ON . . . ZIKA AND THE OLYMPICS

**CAN WE RUN RINGS ROUND ZIKA?**

Infectious disease specialists seem to think so. They estimate that, in a worst case scenario, three to 37 of the 500 000 people travelling to Rio for the 2016 Olympic Games (5-21 August) and Paralympic Games (7-18 September) will bring the Zika virus back to their home countries.

**CAN I DRESS LIKE AN ATHLETE?**

I'm afraid not. There's currently no vaccine or drug to prevent Zika virus infection, so avoidance measures are the order of the day. That means ditching the shorts and vest for long trousers and long sleeved shirts and spraying exposed skin with an effective mosquito repellent (20-50% DEET). When indoors, use air conditioning and keep windows and doors shut. The game plan should also include practising safe sex and avoiding conception during the games and for eight weeks after returning home.

**SO, GO ARMED WITH A GIANT BOTTLE OF REPELLENT?**

Actually, no. If you're heading for Rio take small bottles of mosquito repellent below 100 mL so that you can spray yourself as soon as you get off the plane. Olympic venues will have airport-style security with limits on the volume of liquids you can carry.

**WHO SHOULD BOW OUT?**

If you're pregnant or planning to conceive in the near future, any area with active Zika virus transmission is off limits because of the confirmed risk to fetal neural development. If you have an immune condition or are taking immunosuppressants you should get specialist advice because of the potential risk of Guillain-Barré syndrome.


**I HEAR THAT HANGING A CHICKEN OVER THE BED CAN HELP**

Recent research suggested that malaria transmitting mosquitoes actively avoid chickens. But a bed net is a better option. And make sure that you sleep under a net for daytime naps when *Aedes* mosquitoes are most active. Better to eat the chicken, but make sure it's piping hot: food poisoning is a greater risk in Brazil than contracting Zika.

Susan Mayor, London Cite this as: *BMJ* 2016;354:i4133

# Robotic surgery proves effective for prostate cancer

MARK THOMAS

**Robot assisted laparoscopic prostatectomy has increased rapidly since 2000, but comparisons with open surgery have been limited**

Robotic prostatectomy has achieved similar outcomes to open surgery in removing cancerous tissue and preserving urinary and sexual function in men with localised prostate cancer, early results from a study to compare these two approaches have shown.

The study recruited 326 men (aged 35 to 70) with newly diagnosed localised prostate cancer who had chosen to be treated with surgery. They were randomly assigned to robot assisted laparoscopic prostatectomy or open radical retropubic prostatectomy, led by two surgeons at the Royal Brisbane and Women's Hospital, Brisbane, Australia. Use of robotic surgery for prostate cancer has increased rapidly since its introduction in 2000, but trial data comparing the two surgical approaches have been limited.

**SURGERY RATES**

Men undergoing open surgery had higher rates of postoperative complications (9%; 14/166) than those having robotic surgery (4%; 6/163)

Results from the study, reported in the *Lancet*, showed similar rates of positive surgical margins, with cancer cells along the edge of the excised tissue when examined under

# Money woes hit NHS quality and safety drive

**Most trusts have now accepted new control totals for this year's spending, but for many this only postpones a crisis, comments Richard Vize**

The announcement last week by NHS England and NHS Improvement of a "reset" of finances to try to cut deficits, as well as the accusation that 63 trusts had grown their pay bill excessively, can be seen as the end of the quality and safety policy drive that followed the Mid Staffordshire scandal.

### Changing priorities

When Jeremy Hunt succeeded Andrew Lansley as health secretary for England, his determination to obliterate discussion of health reforms by attacking Labour's record on quality meant that clinicians and managers quickly concluded that running up deficits by recruiting staff was preferable to being identified as "the next Mid Staffs." The safety debate quickly morphed into more staff being equated with higher care standards, while years of poor workforce planning and stagnating pay left trusts in a bidding war to employ unsustainable numbers of nurses and doctors through agencies.

Meanwhile, funding for treatment episodes has been reduced under the guise of efficiency savings as demand rises. Acute trusts ended last year overwhelmingly in deficit, and increasing numbers of clinical commissioning groups are in trouble.

As NHS England's chief executive, Simon Stevens, has mentioned, central bodies are being forced to drive through funding levels they never signed up to: the aim set out in the *Five Year Forward View* in October 2014, of 2% annual efficiency gains, assumed sustained social care funding and investment in prevention. Both have been cut substantially.

NHS England and NHS Improvement said that the new measures were intended to "restore financial discipline"—hinting that sloppy management is as much to blame as underlying pressures.

**FIREWORKS AS PARLIAMENT HEADS FOR RECESS**

- ON 21 JULY the Department of Health published its annual accounts, which showed that it almost breached its £118.3bn budget for 2015-16. An unexpected £417m in national insurance contributions turned a potential £207m deficit into a £210m surplus.
- MEG HILLIER, chair of the Public Accounts Committee, admonished the health secretary, Jeremy Hunt, for

As part of the reset, five trusts have been put into special measures, but dozens more could easily have joined them; some will. The special measures regime—with an improvement director and with specialist and peer support aiming to deliver "accelerated action" to turn the financial position around—forces NHS Improvement to share ownership of the problem. It is certainly preferable to simply

the microscope. One in 10 (10%; 15/166) men undergoing open surgery had positive margins, compared with 15% (23/163) of those having robotic surgery (P=0.21).

**Urinary function**

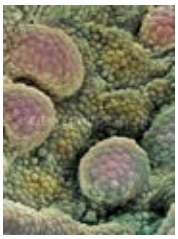
Study participants reported similar urinary function scores at 12 weeks with the two surgical approaches (urinary domain of Expanded Prostate Cancer Index Composite (EPIC) score 83.80 with open surgery *v* 82.50 with robotic surgery; P=0.48). Sexual function scores also showed no significant difference 12 weeks after surgery (sexual domain of EPIC 35.00 *v* 38.90; P=0.18).

Men undergoing open surgery had higher rates of postoperative complications (9%; 14/166) than those having robotic surgery (4%; 6/163) (P=0.052). Intraoperative adverse events were also more common with open radical prostatectomy (8% *v* 2%). Patients who underwent open surgery spent longer in hospital after their procedure, but both groups had the same number of days absent from work.

The lead study author, Robert "Frank" Gardiner, from the University of Queensland Centre for Clinical Research, Brisbane, said, "Our randomised trial, the first of its kind, found no statistical difference in quality of life outcomes between the two groups at 12 weeks' follow-up. Patients are now being followed up for a total of two years in order to fully assess the longer term outcomes, including on cancer survival."

Susan Mayor, London

Cite this as: *BMJ* 2016;354:i4150



**One year onocological outcomes of the study are being eagerly awaited**

**Patients are being followed up for two years to assess longer term outcomes, including on cancer survival**

publishing the accounts on the day parliament rose for the summer recess. "This does not allow MPs to consider the accounts before recess and smacks of an underhand attempt to cover up the poor state of finances in your department," she wrote.

- ON THE SAME DAY, the NHS put its largest trust, Barts Health NHS Trust, into financial special measures, along with Croydon, Norfolk and Norwich, North Bristol, and Maidstone and Tonbridge.
- NINE CLINICAL COMMISSIONING GROUPS (CCGs) were also put into special measures (Coventry and Rugby, Croydon, East Surrey, Enfield, North Somerset, North Tyneside, South Gloucestershire, Vale of York, and Walsall).

criticising trusts from the outside, but it will not solve the big picture.

Under heavy pressure from NHS Improvement most trusts have now accepted new control totals for this year's spending, but for many this only postpones a crisis. They must either brace themselves for intervention by NHS Improvement for still breaching their control total or make substantial numbers of clinical posts redundant. This, in turn, invites criticism from the Care Quality Commission for harming service quality.

The chronic financial problems in the acute sector are throttling investment in community services, which are essential to securing the NHS's long term future. The "reset" announcement does little to help.

Richard Vize, London

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**FIVE MINUTES WITH . . .**

# Ivan Oransky

The cofounder of Retraction Watch says that the stories behind scientific misconduct are too good to miss

"Retraction Watch got started the year after my cofounder, Adam Marcus, broke a big story about Scott Reuben, an anaesthesiologist who ended up going to jail—technically for healthcare fraud but really for scientific misconduct. He did research on Celebrex and pain control, but in more than 20 studies he made up patients.

"I'd always found retractions to be a good source of stories. One of the big reasons we launched Retraction Watch is because we saw so many retraction notices that were unclear. Sometimes the whole notice is, 'This article has been withdrawn by the author.' For a journalist, that's like catnip.

"One summer afternoon I was on the phone to Adam and said, 'What if we start a blog about retractions?' He said, 'Sure.'

"Just two weeks after starting the blog we wrote a post about a strange letter in a journal by a South Korean virology researcher, who said that he'd read a passage in the Bible about how Jesus cured a woman of some kind of illness. The researcher wrote, 'I know what it was. I can tell it was the flu.' And everyone said, 'What? How much more do you need to be wrong with this? This was 2000 years ago. What did you do, exhume her?'

"The journal retracted the letter. It turns out that the guy meant it in a light hearted way. A National Public Radio affiliate picked up our story, and then I'm on the radio talking about Retraction Watch.

"Another thing that happened soon after that was the Marc Hauser case. He was at Harvard and studied monkey learning, and it turned out that he monkeyed with the findings and his grad students blew the whistle on him. Carolyn Johnson of the *Boston Globe* reported on it, and we picked up the story. We got a few scoops and gave our own analysis.

"WHAT? HOW MUCH MORE DO YOU NEED TO BE WRONG WITH THIS? THIS WAS 2000 YEARS AGO. WHAT DID YOU DO, EXHUME HER?"

"Several people have gone to jail now for scientific misconduct.

"We're now creating a database of the reasons for retractions, whenever we can find them."

Jeanne Lenzer, New York

Cite this as: *BMJ* 2016;354:i4134

# Junior doctors will stand together, either to strike or to make new contract work

Ellen McCourt, the new chair of the BMA junior doctors committee, tells **Abi Rimmer** that it is vital for junior doctors to remain united

Ellen McCourt chaired her first meeting of the BMA junior doctors committee on 6 July, the same day the government announced that it would be imposing a new contract on junior doctors in England. The government's announcement came after 58% of junior doctors taking part in a BMA referendum voted to reject the contract.

McCourt was elected to the post after the previous committee chair, Johann Malawana, stood down in response to the junior doctors' decision to reject the proposed contract. Malawana had argued that the new contract was a good deal for juniors.

McCourt said that one of Malawana's biggest achievements was to unite junior doctors through the contract dispute, a unity that she will work hard to maintain. "Johann came in a year ago and galvanised a profession. He brought people together, and that baton has now been handed over to me," she said. "I face similar challenges, to maintain that unity and move us forward, and, once we have some direction from the members of exactly what they want us to do next, it will be important for us to remain united, stand together, and take forward their viewpoint."

After McCourt's appointment as chair of the committee, the BMA sought to gauge the junior doctors' views on the contract by launching a survey, which closed on Monday 25 July. It covered a broad spread of issues, McCourt said, such as asking junior doctors whether they wanted to take further industrial action or whether they wanted to be involved in implementing the new contract.

She said, "It covers the full range of options to really find out what members want us to do, so that it's not me coming in and dictating a course of action. We're a membership organisation; we need to know what junior doctors want us to do next."

Having attended a number of road shows explaining the new contract, McCourt said that it was difficult to know junior doctors' appetite for further industrial action. "What was clear is that doctors were prepared to stand behind their colleagues," she said. "But, on a more personal level for the individual, there was a very mixed group of opinions as to whether industrial action or involvement in implementation was the right road to go down."

She added, "That said, people remain united behind each other, so if there was a clear majority one way or the other junior doctors would stand behind that group of people."

If junior doctors called for further changes to the contract, McCourt believes that there would still be room for further negotiations with the government despite recent political upheaval.

She said, "When Jeremy Hunt chose to impose the contract he stated that his door was always open, and my response to that is that we are always willing to talk.

"With a list of key concerns from juniors we will want to be walking back through that door and saying, 'This is what junior doctors need, this is what junior doctors are worried about, this is what they want to achieve to have a safe and fair contract.' So if his door is open we will be there with our list."

The implementation of the new contract is due to start in October, with third year specialty trainees (ST3) in obstetrics set to be the first junior doctors affected. Despite the relatively short timeline, McCourt was confident that junior doctors could continue to fight for a contract they believe in.

She said, "We've been told several times over the past 12 months, 'The government will never come back and talk to you, you'll never be able to do this, junior doctors won't take strike action, they definitely won't take a full

**"Once we have direction from the members of what they want us to do next, it will be important for us to remain united"**
—Ellen McCourt

## FIVE PROBLEMS WITH LEADERSHIP IN THE NHS

**A report by the Institute of Healthcare Management calls for urgent action to tackle a "leadership crisis" in the NHS. Here are five issues the institute identifies.**

### 1 VACANCIES

Many top level NHS posts are unfilled, and trusts are operating a "revolving door" of senior staff. A third of NHS trusts have vacancies for key leaders at board level or have interim people in post, and the average tenure of an NHS chief executive is two and a half years.

### 2 EXPECTATIONS

Aspiration to top level NHS positions is high among management and leadership trainees, but many are being put off by "unrealistic demands" and believe that they wouldn't be empowered to make changes once in post.

### 3 PRESSURE

Leadership positions have become "less attractive" amid rising financial pressures, perceptions of a "blame culture," the burden of regulation, and increased political exposure. Many talented "second tier" leaders are unwilling to step into the firing line.

### 4 FREEDOM

The institute surveyed students in health and care manager and leadership courses. Of the 111 respondents, most said that they would want more freedom to innovate and implement change when they took on leadership posts.

walk-out, you'll definitely not force the government to come back [to negotiations].' And we've proved them wrong at every stage."

She added, "The time line is ticking on, and the group of obstetric ST3s who will move on to the contract in October are understandably very worried about it, but we've proved this year that when junior doctors stand together we can achieve things that people never thought were possible."

Abi Rimmer, BMJ Careers
arimmer@bmj.com

**5 DIVERSITY**

Half of trainee mangers said that health and care leadership did not reflect the diversity of the workforce. Only 15% said that it was as easy for black and minority ethnic managers to reach top posts as it was for their white counterparts.

# NHS must improve relations between junior doctors and government

NHS organisations should improve junior doctors' working and training conditions to try to repair relations between the profession and the government, NHS England's national medical director has said.

Speaking at an evidence session of the parliamentary health committee on 19 July, Bruce Keogh told MPs that he wanted to help change the bad feeling between the two parties.

Relations have been strained because of the recent industrial dispute over a new contract for junior doctors in England, which led to a full strike by BMA junior doctor members in April.

The new contract, which will be imposed later this summer, was rejected by most BMA members who voted in a ballot.

Keogh said, "I am concerned about morale in the medical profession at the moment. The junior doctors are a young generation with a different set of expectations to the older generation, but they have an equally strong, if not stronger, sense of values and are highly committed to improving patient care.

"Those values and their desire for improvement have amplified their growing discontent about issues related to their training and, in particular, the way they are treated by some NHS organisations. This has led to a real perception of not being valued."

Matters had become "very complicated" when contract discussions were linked to weekend mortality, which had "unleashed simmering discontent," Keogh said.

Pushed on the issue of weekend mortality rates—from a study published in *The BMJ*—Keogh said that the figures had been "misused" by all sides.

Nevertheless, now that the contract was being imposed, he added, "there is still a lot to do to improve the working lives of junior doctors."

After discussions with junior doctors and colleagues, Keogh said that he had decided on several steps that could be taken to help junior doctors, including:

- Making sure that periods of training are longer than four months
- Improving the quality of the annual review of competence progression
- Significantly increasing the flexibility of training, allowing for a person's mobility and area of training
- Allowing juniors to see where their placements are going to be earlier and to see their rotas sooner
- Having long term training supervisors or mentors
- Having streamlined induction and mandatory training, as well as support for transitional periods, and
- Improving facilities on site, such as catering for those working at night.

Keogh said that he expected various bodies to take action on these points including NHS England, acute trusts, Health Education England, NHS Employers, and NHS Improvement.

The issue of the UK leaving the EU following the recent referendum was also discussed at the evidence session, during which Keogh expressed some concerns about its impact on research and academia.

"A number of individuals have indicated that they are not that keen on coming to jobs in the UK—people with significant academic backgrounds—and we are already hearing of collaborations that are being put on ice while this uncertainty is being resolved," Keogh said.

Adrian O'Dowd, BMJ Careers
adrianodowd@hotmail.com

**There is still a lot to do to improve the working lives of junior doctors**
—Bruce Keogh

# London 2012 relived

A recent BBC documentary, *One Night in 2012*, told the story of Danny Boyle's dazzling opening ceremony for the London 2012 Olympic games, which included a sequence celebrating the NHS, complete with dancing doctors and nurses. With the Rio Olympics kicking off on 5 August, NHS staff who volunteered at London 2012 reflected fondly on their experience of the opening night.

Joe Cosgrove, a consultant in anaesthesia and intensive care at Freeman Hospital in Newcastle upon Tyne, volunteered as a crowd doctor that night and throughout the games. His role was to respond to any illness or injury within the crowd during the events, supported by a team of nurses and other staff.

"It's something I'm very proud of," he tells *The BMJ*. "Everyone was blown away by the opening ceremony and I think it lifted everybody," he says.

"It reinforced your own views about why you do the job you do and also why you'd volunteer to do the Olympics as well, because there were a lot of experienced people there from nursing and medicine but all of us were volunteers. It's a reflection of the mindset of a lot of people that work in healthcare that they would volunteer for something like that. There is a selflessness to their motives."

**It's a reflection of the mindset of a lot of people that work in healthcare that they would volunteer for something like that**
– Joe Cosgrove

Alongside dancing medics, Boyle's ceremony included a tribute to Great Ormond Street Hospital in London, and nine long term patients at the children's hospital were given the chance to appear in the ceremony.

Sarah Carmichael was one of two nurses from Great Ormond Street who accompanied the children, and still buzzes with excitement as she recalls how the evening unfolded.

"It's been four years now, I don't think I'll ever forget that day," she reflects. "It was very unique. Obviously I'd never expected to do anything like this being a nurse. The stadium was so huge, the lights [and] the music were amazing. It was incredible to be a part of it.

"We all had little ear pieces so we could listen to the person directing everyone on the floor. When we were told to, we all walked out onto the big grass hill and waved. All the kids were in a line, and they absolutely loved it."

Gareth Iacobucci, news reporter, *The BMJ*

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STEVE RUSSELL/GETTY IMAGES

ILLUSTRATION: DUNCAN SMITH

Kalipso Chalkidou, 39, is the founding director of NICE International, set up to spread globally the approach to value for money in medicine pioneered by the National Institute for Health and Care Excellence. Born in Greece, she gained her doctorate in molecular biology of prostate cancer from the University of Newcastle. She believes that universal access to healthcare in low and middle income countries can be achieved only by setting priorities rationally through health technology assessment, reinforcing her argument with many examples of misallocation. "But you cannot impose evidence informed policy making," she admits. "The political will has to be there."

**BMJ CONFIDENTIAL**

# Kalipso Chalkidou
# Internationally NICE

**What was your earliest ambition?**
To become a train driver. Still unfulfilled (for now).

**Who has been your biggest inspiration?**
Around the time I joined medical school it was Che Guevara. I was fascinated by his ability to overcome his physical weaknesses to do what he set his mind to doing (he had asthma but still excelled in sports). A real hero.

**What was the worst mistake in your career?**
Thinking that I'd make a great surgeon. My fine motor skills aren't very good—but I realised it early enough and changed career tack.

**What was your best career move?**
Setting up NICE International. It gave me the chance to work with the coolest people, visit amazing places, and appreciate how much we have in common as humans, including health policy.

**Bevan or Lansley? Who has been the best and the worst health secretary?**
I haven't lived through many of them in the UK. Bevan's NHS inspired and is still inspiring generations of policy makers, clinicians, and citizens worldwide.

**Who is the person you would most like to thank, and why?**
Tony Culyer, for being the brightest, most articulate, most obsessive with split infinitives, and most generous person I can call my friend. And Peter Littlejohns, for giving me my first job at NICE and believing in me ever since.

**To whom would you most like to apologise?**
My husband, Duncan, because I'm constantly working when he's trying to have a meaningful conversation with me.

**If you were given £1m what would you spend it on?**
I'd give it to HITAP, the Thai equivalent of NICE, to expand its amazing work.

**Where are or were you happiest?**
During summers as a little girl on the coast in northern Greece, at the foothills of Mount Olympus. Three summer months full of incredible adventures.

**What single unheralded change has made the most difference in your field?**
Health economics: the extra-welfarist kind favoured by Tony Culyer and Karl Claxton, with their QALYs and thresholds and all.

**Do you support doctor assisted suicide?**
Yes, primarily and selfishly for my own benefit, should I ever need to use it.

**What book should every doctor read?**
*On Liberty* by John Stuart Mill, especially the second chapter, on liberty of thought and discussion. The medical profession the world over needs to learn to accept challenge—invite it, even—from patients, scientists, and commissioners.

**What is your guiltiest pleasure?**
Emailing relentlessly, and trying to minimise the unread emails in my inbox.

**What is your pet hate?**
Political correctness. It makes life more boring than it has to be.

**What would be on the menu for your last supper?**
Fried vegetables with meatballs with vinegary and garlicky tomato sauce, cooked by my grandmother…and a glass of tsipouro (those interested will have to search online).

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EDITORIAL

# Dietary therapy for irritable bowel syndrome

## High expectations for low FODMAP diets

Irritable bowel syndrome (IBS) is a common disorder of the digestive system, affecting about 10% of the global population.[1 2] The condition has no definitive biomarker or cure, but various drug treatments have been introduced in recent years, including antibiotics and agents that affect motility through fluid secretion or the enteric nervous system.[3 4] Despite these advances, perhaps the most popular option among patients in recent years has been a dietary approach, the "low FODMAP diet."

The term FODMAP was first coined by Gibson and Shepherd in 2005, referring to a new dietary class comprising fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.[5] The authors identified a list of foods that are highly fermented but poorly absorbed, leading to the expansion of ileocolonic bacteria. This broad dietary class includes fructose (in fruits and sweeteners), lactose (in dairy products), fructans (wheat based products), galacto-oligosaccharides (legumes), and polyols such as xylitol and mannitol (fruits and artificial sweeteners).

### Face validity

A dietary approach to treating irritable bowel syndrome has intuitive appeal. Most patients with this condition report that their symptoms are exacerbated by specific foods or are temporally correlated with eating in general.[8] There is also a pathophysiological rationale, given the effect of these foods on the production of gas and short chain fatty acids, and the effect of the fatty acids on motility.[8] Indeed, evidence

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**Given the sheer number of restricted items in a low FODMAP diet, we should consider this diet a potent combination of dietary prescriptions**

is accumulating that this strategy is effective. A randomised crossover trial of 30 patients in Australia with irritable bowel syndrome found that those prescribed a low FODMAP diet had significantly lower (improved) gastrointestinal symptom scores on a visual analogue scale compared with those prescribed a typical Australian diet.[9] A subsequent systematic review and meta-analysis identified six randomised trials of the low FODMAP diet, with a pooled analysis finding a significant decrease in symptom severity scores.

The rise of the low FODMAP diet for irritable bowel syndrome has had a ripple effect on another condition, non-coeliac gluten sensitivity. People with this syndrome, which has uncertain pathogenesis and natural course, report both intestinal (eg, bloating, abdominal pain, and altered bowel habits) and other symptoms (eg, fatigue and headache) when exposed to dietary gluten but have had coeliac disease definitively ruled out. A randomised trial examining the syndrome found that affected patients had a greater exacerbation of symptoms when given gluten than when given placebo, providing initial justification that non-coeliac gluten sensitivity is a distinct clinical entity.[11] However, in a second trial, when patients with this syndrome were put on a low FODMAP diet before randomisation, introduction of gluten made no difference to symptoms relative to placebo. The investigators concluded that the apparent improvement reported by patients who start a gluten-free diet may be due to restricting FODMAPs.[12]

The fact that the low FODMAP diet seems effective is welcome news for patients with irritable bowel syndrome and their doctors. However, the long term effectiveness of this diet is unknown and given the restrictive nature of the diet, it may be hard to stick to. Even among patients who can adhere to the diet in the long term, it is not known whether it promotes an ileocolonic microbiome conducive to long term health and symptom control. There is no evidence that the low FODMAP diet is harmful, although inadequate vitamin and mineral intake is a theoretical concern given its overlap with the gluten-free diet.[15]

### Pick and mix

Given the sheer number of restricted items in a low FODMAP diet, we should consider this diet a potent combination of dietary prescriptions. The full spectrum of FODMAPs may not be responsible for symptoms in a given patient, or even in most patients. Future studies should consider breaking down this list of restrictions into component parts to determine whether a less restrictive dietary approach could be effective. A positive result on fructose breath testing might allow the restriction of fructose rather than a full low FODMAP diet. In addition, a positive result may predict response to the FODMAP diet.[16] An experienced dietitian can help manage patients on a low FODMAP diet and facilitate controlled reintroduction of individual components. Ultimately, irritable bowel syndrome may prove to be a heterogeneous group of conditions that respond to a range of dietary strategies. It is likely that one size does not fit all.

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## Why government must negotiate a better deal for publicly funded research

The investigation by *The BMJ* and Cambridge and Bath universities into the availability of breakthrough hepatitis C drugs raises important questions for NHS England about access to lifesaving drugs.[1] But why are medicines so expensive in the first place? The pricing strategy of Gilead for sofosbuvir (Sovaldi) and ledipasvir-sofosbuvir (Harvoni) raises questions that go well beyond the UK.

*The BMJ*'s investigation is just an example of a more general problem. What is the right price to pay for a particular drug, and how should this be determined?

Pharmaceutical innovation should be structured to focus on unmet health needs globally and delivers therapeutic advances that are affordable and accessible to all,[2] not just profitable for manufacturers. This requires an approach that directs effort towards therapeutic innovations over "me too" drugs, and a transparent financing and pricing structure, focused on access, and reflecting the collective investment and risk taking involved.

Drug companies have often ignored the collective element of innovation and argued that their research and development investment justifies the extraordinarily high prices for some medicines, despite the lack of transparency. The Drugs for Neglected Diseases initiative has documented much lower drug development costs,[3 4] and several authors have shown the extent to which taxpayer funded investments subsidises those costs.[5] In the US alone, tax payers fund $32bn a year of research and development expenditure through the National Institutes of Health (NIH).[6]

### Value judgment

Sofosbuvir and ledipasvir, the drugs on which *The BMJ* investigation is based, relied on early stage funding from the NIH and the Veterans Administration.[7] Sales of the two drugs were around $12bn in 2014,[8] far in excess of the $880.3m which Gilead reported for sofosbuvir related trials from 2012 to 2014,[7] showing a complete disconnection between price and development costs.

As high prices are hard to justify based on research and development costs, drug companies have instead argued that their prices are proportionate to the intrinsic value of the drugs—that is, the costs to society if a disease was not treated, or if treated with the second best therapy available. "Price is the wrong discussion," declared Gilead's executive vice president, Gregg Alton, responding to criticism over the price of sofosbuvir, "value should be the subject."[9]

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But there is no consistent link between a drug's price and the associated medical benefit.[10] A study published in 2015 in the *Journal of Economic Perspectives* examining a sample of 58 cancer drugs approved in the US between 1995 and 2013, shows that the increasing trend in the price of these medicines is not explained by the survival benefits they provide. Over two thirds of new medicines reaching the market do not represent any therapeutic advance for patients, with many patents based on a reshuffling of old combinations or additional uses for existing ones.[11]

### A better way

An effective pricing system should ensure accessibility and reflect the public contribution so taxpayers don't pay twice, through publicly subsidised research and high priced medicines. In such a system, drug prices do not need to be so much higher than manufacturing costs. We could, for example, limit patents on new medicines (the current source of company profits) and instead establish a competitive prize system that rewards well targeted pharmaceutical innovation. This would allow widespread access to drugs at competitive prices through generics, while pushing drug companies to focus their energy on delivering innovations that fulfil real medical need. In any case, patents should not be so upstream to affect scientific research, and should remain relatively narrow so as not to close off future discoveries.[12] They should foster innovation, not stifle it.

Importantly, drug pricing must be transparent, so that governments can negotiate for better value and ensure that the prices of new drugs reflect the burden of financial risk borne by the taxpayer. Public funders could retain the lion's share of intellectual property rights (patents) produced by public research so that spillovers through licensing can be better managed to foster diffusion. In the US, the 1980 Bayh-Dole Act that allowed publicly funded research to be patented includes a clause enabling the government to cap the prices of drugs that are largely publicly funded. The US government has never exercised this right.[13]

The international debate about unsustainable drug prices, including those for hepatitis C drugs, offers an opportunity to rethink the therapeutic innovation ecosystem—the direction and the accessibility of the drugs that result. Realising that government has power to actively shape and create markets, and not just remain on the sidelines fixing broken ones, is the first important step to reaching a better deal.[14 15]

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# A pill too hard to swallow: how the NHS is limiting access to high priced drugs

A joint investigation by *The BMJ* and Cambridge and Bath universities uncovers how NHS England tried to limit access to expensive new drugs. **Jonathan Gornall, Amanda Hoey,** and **Piotr Ozieranski** report

Highly priced medicines are challenging health systems around the world in unprecedented ways. And none more so than the new sofosbuvir based antiviral drugs introduced by Gilead Sciences in 2014. Offering greatly reduced treatment durations and high cure rates, these medicines hold out the real prospect of eliminating hepatitis C in countries where they are widely administered, with all that implies for long term savings in costs.

But launch of these drugs has ignited a global debate about high priced medicines. With launch prices ranging from around $90 000 (£69 000) per patient in the US to almost £35 000 in England and €41 000 in France,[1] they have sparked a US Senate investigation (box), and been raised at both the G7 and G20 summits.

The hepatitis C medicines have intensified tensions between drug companies' duty to put shareholders' interests first and governments with limited health resources. Sofosbuvir is not the first high priced medicine. But because hepatitis C affects so many people it has become a pill too hard to swallow for budget planners. Rationing, in their view, became inevitable.

Now there is new evidence about the extent to which hepatitis C treatments have challenged the NHS and the National Institute for Health and Care Excellence (NICE) in England.

In a joint investigation, *The BMJ* and researchers from the University of Cambridge and the University of Bath, show how NHS England, unable to budget for broad access to these drugs, tried to alter the outcome of the NICE process and, when it failed, defied NICE's authority by rationing access to the drugs.

In interviews with clinicians, patient groups, and drug company representatives, a picture emerges of how NHS England failed to plan ahead for expensive drugs, exaggerated the numbers likely to come forward for treatment and the financial burden for them in its submissions to NICE, and, in a "shroud waving" exercise, claimed thousands of other NHS patients would die if NICE gave the go ahead to the hepatitis C drugs.

The case shows how high prices for high prevalence diseases places huge stress on health systems and reveals the limitations of conventional cost effectiveness analysis. Although NICE may deem such medicines to be cost effective, the NHS is ill equipped to meet the costs. This leads to conflict and damaging delays for patients. It also reveals an urgent need for better deal making, transparent pricing, and new payment models.

**160 000** people in England have chronic hepatitis C but NHS England is only treating **10 000** per year with the new drugs

### Hepatitis C medicines

By the end of last year, NICE had approved widespread use of two Gilead drugs for hepatitis C. First came sofosbuvir (Sovaldi),[2] in February 2015, followed by the oral combination ledipasvir-sofosbuvir (Harvoni) in November.[3] Competitor treatments from drug companies AbbVie and Bristol-Myers Squibb were also approved.[4]

These drugs should have been widely available to NHS patients after a statutory 90 days.[5] But this has not happened.

Before the NICE process was complete, NHS England made sure that the sickest patients— people with liver failure who might die before the guidelines were issued— were treated. In 2014, it set up the Early Access Programme for patients with advanced liver disease,[6] followed by a new £150m fund in June 2015 to treat patients with cirrhosis of the liver caused by chronic hepatitis C— nearly 5000 people in total.[7]

But according to Public Health England an estimated 214 000 people have chronic hepatitis C infection in the UK, 160 000 of whom are in England.[8] Most are still waiting for treatment with the new drugs.

In apparent panic over high prices and affordability, NHS England deployed delaying tactics to block timely access to the hepatitis C drugs. It delayed NICE recommendations on sofosbuvir by requesting a three month extension to implement the guidance, on top of the mandatory 90 days, saying it needed time to set up a proper database to audit patients.

NHS England went on to try to completely block Harvoni and two other competitor drugs by questioning the level of evidence for the new treatments. NICE stood its ground and, in November 2015, published guidance recommending these drugs for most patients with hepatitis C. But NHS England has restricted use of the new drugs by imposing quotas on clinical teams.

NHS England says its delivery of the drugs is within NICE guidance. Expert clinicians do not agree and are angered by its tactics.

In April 2015, one member of NHS England's six person clinical advisory group resigned in protest at NHS England's behaviour.

"I pulled out of the advisory group on principle, because of everything that was going on," said Andrew Ustianowski, a consultant in infectious diseases at Pennine Acute Hospitals NHS Trust.

BELLE MELLOR

## IS COMPANY PRICING TO BLAME?

Faced with the intensifying criticisms, NHS England has highlighted Gilead's pricing as the key reason why treatment was being delayed. A press release in March 2016 said that "making faster progress for patients in eliminating this disease will depend on pharmaceutical companies making them more affordable."[12]

This echoed major criticisms of Gilead's pricing strategy, best documented in an 18 month investigation by the US Senate Committee on Finance into the pricing and marketing of sofosbuvir. Legislators concluded that the company had adopted a strategy "designed to maximise revenue with little concern for access or affordability."[28] This was made evident by the company's income jumping from about $10bn in 2013 to over $32bn in 2015.

So why didn't NHS England strike a better pricing deal with Gilead? It refused to disclose how much it had budgeted for the new hepatitis drugs in 2016-17, "to avoid prejudice to the ongoing tendering processes and commercially confidential prices agreed." Nor would it say how much it was paying Gilead for the drugs as "it might inhibit reductions that pharmaceutical suppliers to the NHS are prepared to make."

NHS England isn't able to enter into a risk sharing deal similar to that agreed between Gilead and the Australian government in December 2015. There, the government is investing $A1bn (£600m) over five years "to give all Australians with hepatitis C [estimated at 230 000 people] access to cures."[15]

In England, negotiations with pharma are the remit of the Commercial Medicines Unit, reporting to the Department of Health, which runs regionalised tenders of different periods. A spokesperson for NHS England declined to say why it had deemed a deal on the Australian model inappropriate for England but hinted that this could change. Over the next eight months, following discussions with the Commercial Medicines Unit, it was "exploring the potential for a longer term strategic procurement for a supply agreement with the industry to improve the affordability of and access to treatment further."

There were, he says, "multiple things," but the final straw was an NHS England response to the NICE consultations.

"They said the advisory group was agreeing that the treatment centres around the country hadn't got the capacity and that's wrong—of course there's capacity to treat more people. I just didn't want to be associated with delaying patients getting access to the treatments."

Steve Ryder, a hepatologist from Queen's Medical Centre, Nottingham, chair of advocacy organisation HCV Action, and a fellow member of the hepatitis advisory group, had other issues with NHS England.

"Its position was that the hepatitis C drugs were unaffordable and the figure they quoted in the NICE submission was something like £2bn, which was clearly fantasy," he said. "The assumption to come up with that figure was that you had no discounts on any of the drugs and that every person with hepatitis C in England would come forward that year for treatment, so it was completely ridiculous."

NHS England is also accused of pursuing the broader agenda of trying to hamper NICE's ability to impose budget busting drugs on the health service, and of having cynically chosen this battleground because most people with hepatitis C infection are injecting drug users, a marginalised group without a voice.[8]

"The difficulty is that NICE looks at cost effectiveness over a long period and says a drug is cost effective because it's saving people from dying or having problems years down the road," says Ustianowski, "and this is very different from budget impact, which is what NHS England is facing."

As a result, "I think some people in NHS England would love to clip NICE's wings and turn it into a kind of recommendatory rather than mandatory body. And if you are going to choose a fight then choosing this battlefield is quite a sensible thing to do."

### Sofosbuvir appraisal—first struggle to delay access

Although NICE's technology appraisal guidance was published in February 2015, NHS England's request to delay by an extra three months ensured that sofosbuvir was not available until 1 August 2015.

Such a request to delay, in essence because it claimed it wasn't ready for the numbers of patients expected to come forward for treatment, was almost unprecedented. But NICE bowed to it despite almost unanimous opposition from other consulted groups, including the British Association for the Study of the Liver and the British Viral Hepatitis Group, British HIV Association and British Association for Sexual Health and HIV, the British Liver Trust, Haemophilia Society, Royal College of Pathologists, and the Royal College of Physicians.

Gilead Sciences launched its new hepatitis C drugs in 2014. The company's income jumped from $10bn in 2013 to over $32bn in 2015

The Hepatitis C Trust pointed out to NICE that NHS England had known about the technology "for at least 18 months" and it would be "unconscionable that patients should be made to wait simply because NHS England has dragged its feet" It added, "If we are going to change our healthcare resource allocation model to one based on the arbitrary consideration of this year's budget, then this should be debated nationally, preferably through an election manifesto. Either NICE has a mandate to decide resource allocation or it doesn't."

### Harvoni—battle over cost effectiveness and budget impact

Gilead's combination treatment Harvoni was the next hepatitis C drug to pass through the NICE system, along with two competitor treatments, AbbVie's ombitasvir-paritaprevir-ritonavir (Viekirax) and Bristol-Myers Squibb's daclatasvir (Daklinza). They were approved despite persistent attempts by NHS England to persuade NICE to reject them.

On 23 March 2015, NHS England responded to NICE's consultation on Harvoni with a document saying that it didn't believe NICE's proposed recommendations were "in the best interest of the NHS at this time."

NHS England also tried to stop the appraisals and introduce an 18 month delay by saying a new appraisal was needed to compare all three oral drugs at the same time.

In further correspondence, on 1 April 2015, NHS England estimated that if access to the drugs was given to "all patients of all stages of disease," treatment numbers could range from 7000 to 32 000 patients, at an estimated cost of £285m-£772m a year. NHS England acknowledged the higher estimate of 32 000 patients was unlikely but the figures were based on "international examples" where 40% of infected patients had accessed treatment.

NHS England commissioned an analysis of budget impact from the Centre for Health Economics at the University of York. This suggested that if £300m were diverted from the existing budget to pay for hepatitis drugs, 1542 lives would be lost across the rest of the NHS.

These figures were disputed in a joint submission to NICE by the British Society of Gastroenterology, the British Association for the Study of the Liver, the British Viral Hepatitis Group, and the Royal College of Pathologists.

They wrote, "we contest that the true figures are highly affordable and represent excellent value for NHS England."[10]

The clinical bodies added that, in the face of overwhelmingly positive results from trials, NHS England's contention that the evidence for the interventions was inadequate was seriously flawed, and "at odds" with the consensus reached by its hepatitis C clinical reference group and clinical advisory group.

"We believe that if upheld," they wrote, "this challenge to NICE by NHS England would fundamentally alter NICE's role and remit. This would potentially…deny not only hepatitis C sufferers but people with other serious clinical conditions access to highly cost effective therapy."[11]

### New-style rationing

NICE recommended Harvoni on 25 November 2015, with the drug in theory becoming available for all indicated patients by the end of February 2016. But NHS England had saved its most extraordinary manoeuvre until the end of its campaign to stall access to the drugs.

In an apparent attempt to build on the success of its early access programmes, NHS England announced in March 2016 that it would be "doubling the number of treatments to 10 000 patients in 2016-17."[12] But what the celebratory tone of the press release concealed was that the "commitment" to treat 10 000 patients through 22 new "operational delivery networks" was actually a decision to ration the number of patients they could treat.

The new centres were given a "run rate," the maximum number of patients they could treat each month in the financial year 2016-17.[13] Exceed this number, they were warned, and "the dispensing provider will bear the financial cost of treatment."

In fact, the rationing has left many clinicians facing hard decisions and difficult conversations with patients.

"NHS England's view is that it is down to each network to prioritise patients and it envisaged it would be on severity of liver disease," says Ryder. "But once you've treated all the patients with cirrhosis, that's rather difficult, because by definition everybody else doesn't have serious liver disease yet. It's down to the individual physicians, and my practice has been pretty much 'Buggins' turn'—if you turn up to clinic early in the month you are more likely to get treatment immediately than if you turn up later."

A budget impact report suggested that if £300m were diverted to pay for hepatitis C drugs, 1542 lives would be lost elsewhere in the NHS

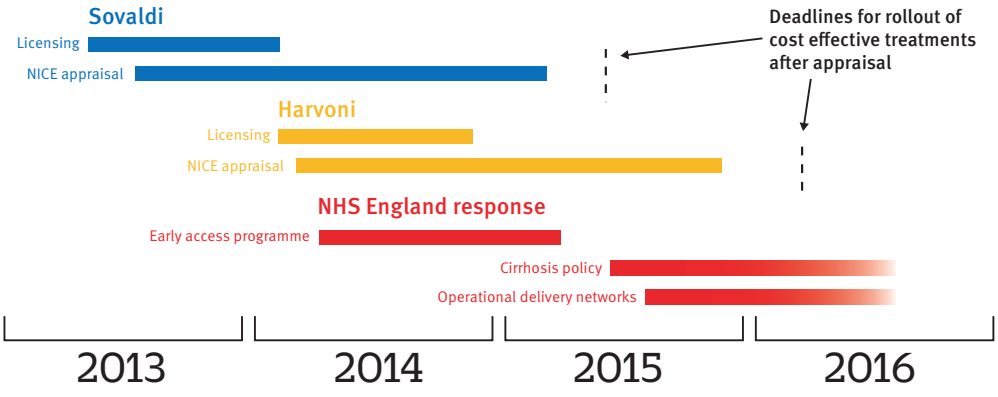
The run rates, says Ryder, "are set entirely to hit NHS financial targets. My own experience is that we have about a third more people who meet the criteria every month than we have [funding] for."

NHS England acknowledged that it considered its "planned roll-out" of the new treatments to be "in line with the NICE guidance," which required networks to prioritise patients with the highest unmet clinical need.

Ustianowski, who runs the operational delivery network for Greater Manchester and East Cheshire, says NHS England's "logistical limits" are overstated. His group of five hospitals have been given a total monthly run rate of just 50 patients, which "is hardly anything," he said. "We could easily do the 50 just in our hospital every month, if not a bit more, but we're better off than some regions…For example, Sussex and Brighton have something like 180 patients for the whole year, which is ridiculous."

Time is not on the side of many patients and last month the Hepatitis C Trust launched legal action seeking a judicial review of the decision to limit access to the new drugs—a decision which, it says, could have repercussions for other patient groups as increasingly expensive drugs become available.

Legal action, said its chief executive, was "a very significant financial risk for us but we absolutely have to stand up for the people we are here to support. We do not want to fight the NHS but we will fight for a fair NHS."[11]

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ANALYSIS

# Betting on hepatitis C: how financial speculation in drug development influences access to medicines

**Victor Roy** and **Lawrence King** argue that the acquisition strategies of drug companies magnify development costs and leave the public paying twice—for research and high priced medicines

**KEY MESSAGES**

- Gilead's $11bn acquisition of sofosbuvir after phase II studies magnified the speculative costs of drug development
- The resulting $35bn in revenue has been primarily directed to shareholders via share buybacks rather than to further research and development
- The public pays "twice," both funding pivotal early research and purchasing the drug at high prices
- Solutions include giving health systems increased power to negotiate pricing and payment models, limiting share buybacks, and testing other ways to encourage and reward drug development

Sofosbuvir based medicines have marked an important breakthrough for patients with hepatitis C infection, offering cure rates of over 90%. The virus is a leading infectious killer globally, disproportionately affecting vulnerable groups such as people who inject drugs or have HIV/AIDS.[1] Even after discounts offered from a US list price of about $90 000 (£70 000) per three month treatment course, however, the cost of these drugs, manufactured by Gilead Sciences, has challenged government budgets and led to rationing. Sofosbuvir's pricing has been at the centre of a global debate over the affordability of prevailing systems of drug development, and the US Senate conducted an 18 month investigation into Gilead's pricing strategy and its consequences for health budgets and patient access.[2]

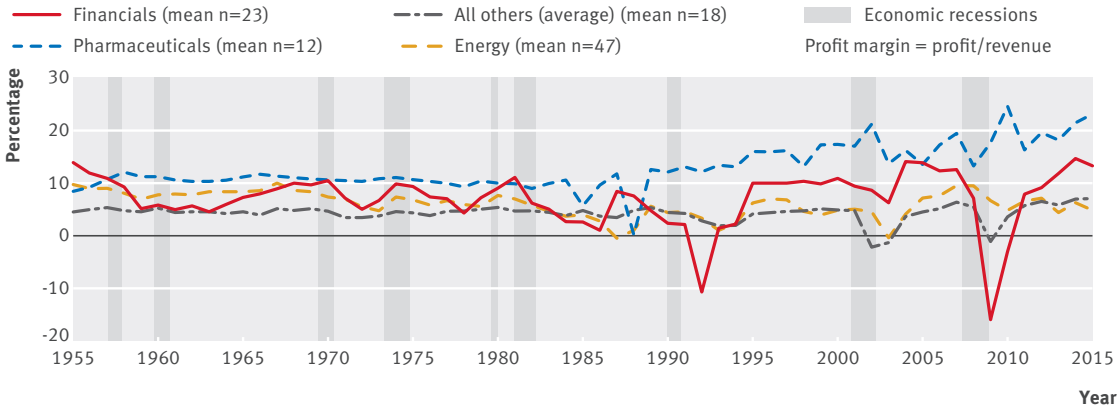
One argument for the high prices has been that the curative drugs represent a major advance in value to patients and health systems. They are indeed more cost effective than many expensive medicines that provide only marginal benefit. Yet the company's ability to charge high prices ultimately relies on monopoly protections via patents, which the industry has long argued are necessary to encourage costly research and development. Critics, however, charge that these costs are exaggerated.[3-5]

We use the case of hepatitis C to highlight another dynamic missing from the debate: the financial model driving large companies and their shareholders. To maximise growth in earnings, large companies like Gilead often enter expensive bidding contests to acquire companies with promising compounds. Subsequent profits are then directed back to shareholders rather than invested in early stage research. This speculative cycle propels the prices of medicines and impedes affordable access for both current and future patients.

BELLE MELLOR

### Bringing sofosbuvir to market

During the 2000s, a small start-up called Pharmasset emerged from a publicly funded laboratory at Emory University to develop sofosbuvir, the backbone compound behind the new class of curative hepatitis C therapies.[6] Raised primarily from venture capital and eventual stock based financing, the company's total reported research and development spending (2003-11) in US Securities and Exchange filings was $271m for sofosbuvir and other failed compounds.[7 8] From this total, Pharmasset reported $62.4m specifically for developing sofosbuvir from preclinical research to phase II trials.[6] At this stage, Pharmasset identified a future budget of $125.6m for taking sofosbuvir through phase III trials and FDA approval, bringing the compound's total past and projected development costs up to $188m.[6]




**Fortune 500 average profit margin by sector over time**

Phase II trials of sofosbuvir showed a more promising cure rate than Gilead's in house prospects.[9] In anticipation of an annual $20bn market in coming years, Gilead acquired Pharmasset for $11bn in November 2011 using cash from previous profits and new debt.[10] Gilead gained approval for sofosbuvir by December 2013 after completion of four phase III registration studies and with the help of the FDA's accelerated approval pathway.[11]

The company has since combined sofosbuvir with a series of in-house protease inhibitors (ledipasvir in Harvoni, for example), aiming to create a single oral regimen that shortens treatment from 12 weeks to under eight weeks for some patients. Though Gilead has not shared the costs of its failed compounds and previous in-house research, the company reported aggregate costs of $880.3m to the US Senate for sofosbuvir based clinical trials from 2012 to 2014.[12]

### Costs of speculative acquisitions

Gilead's function as an acquisition and regulatory specialist in drug development for hepatitis C reflects a strategic preference shaped by financial concerns. Gilead's preference is part of an industry-wide pattern. A 2014 study found that companies deemed to be "winners" earned more than 70% of their sales from products developed by other companies.[14]

The financial sector drives this dynamic by valuing large companies based less on their profits than on the expectations of short term (quarterly and annual) earnings growth. For companies with faltering in-house pipelines the fastest routes to new revenue growth is increasing prices on existing drugs or acquiring compounds that have already proved promising in early stage trials.

In a December 2015 interview with the *Financial Times*, Gilead's executive vice president of research and development, Norbert Bischofberger, elaborated the financial implications of the acquisition based strategy: "Philosophically, we prefer to wait for more certainty and pay more money, which is what we did with Pharmasset, rather than getting something cheap with uncertainty."[15] Indeed, the speculative cost of acquiring sofosbuvir rose far above Pharmasset and Gilead's real expenses in clinical development.

To be sure, large companies operating as investment funds allow for failure and encourage smaller teams of innovators and venture capitalists that are often deemed more effective at pursuing riskier stages of research. However, this acquisition based model presents challenges for drug affordability in two ways. Firstly, the cost of drug development escalates through bidding wars and "racing"—when several large companies pursue similar compounds in the final stages of drug development, often through acquisitions. For example, Gilead competed with several other companies for Pharmasset, bidding up its valuation by nearly 40% in the final weeks before its $11bn acquisition.[16] This also rapidly raised the speculative value of other small start-ups with hepatitis C compounds, with Merck and Bristol Myers Squibb spending $3.85bn and $2.5bn respectively on subsequent acquisitions.[17 18]

Secondly, since companies have patent protected monopolies on new drugs, they can charge high prices to accrue long term profits and make further late stage acquisitions. Data from the US Senate investigation of Gilead revealed that though Pharmasset had initially considered a price of $36 000 for sofosbuvir, Gilead ultimately set $84 000 as its market list price after internal deliberation over multiple factors, including an evaluation of the high prices of previous drugs and how much health systems could bear.[12]

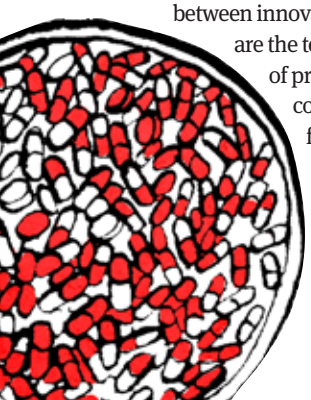
**A strategy of buybacks in the short term could threaten access to future innovations for patients in the long term**

### Uses of Gilead's hepatitis C money

Examining the destination of Gilead's hepatitis C revenue reveals a second form of speculation that distorts the claimed link between high prices and further innovation. By the first quarter of 2016, Gilead had accumulated over $35bn in global revenue from hepatitis C medicines since their launch in December 2013. This revenue is over triple the cost of the initial acquisition of Pharmasset and nearly 40 times the cost of Gilead and Pharmasset's combined reported costs for developing sofosbuvir based medicines.[20] In 2015, the company's revenue from hepatitis C drugs exceeded $19bn, equivalent to two thirds of the $30.4bn budget of the US National Institutes of Health for the same year.[21] Gilead's profit margins of 55% in 2015[21] stand out even in an industry that consistently outperforms its peers. Based on data reported in *Forbes' Fortune 500* list, an annual ranking of the biggest US companies, the pharmaceutical sector has been by far the most profitable of all sectors, with a mean profit margin of 17.44% from 1995 to 2015, compared with an average of 4.34% for all other industries (see above).

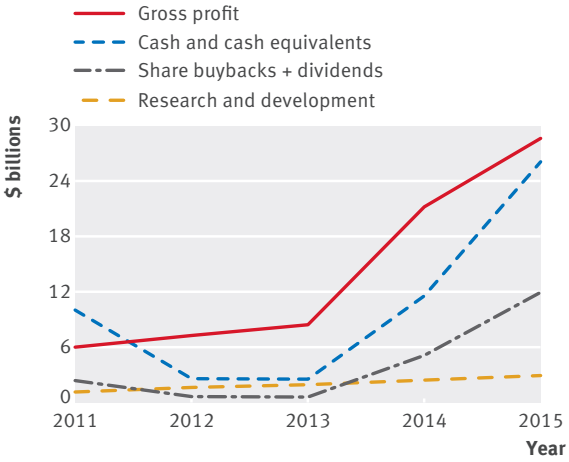
Beyond stockpiling a portion of this money for future acquisitions—Gilead holds nearly $21bn in cash[22] —where have its profits gone? Since the beginning of 2015, the company has announced $27bn in "share buybacks" to be executed over the coming years. Share buybacks, which emerged in the 1980s and peaked in recent years, are a financial manoeuvre whereby a company purchases its own shares to increase the value of the remaining ones.[23 24] The financial community now expects companies to reward shareholders with buybacks, especially when a stock price is thought to be undervalued or other allocations of capital such as long term research projects are deemed to be too risky by executives and investors.[25]

However, this financial strategy reduces investment in early stage research projects crucial for future innovation.[26] Over the past decade, for example, Pfizer directed $139bn to shareholders, primarily via buybacks, compared with $82bn for research and development.[27] In December 2014, Merck spent $8.4 billion to acquire Cubist Pharmaceuticals, a drug developer specialising in combating meticillin resistant *Staphylococcus aureus*. The following year Merck announced the closure of Cubist's early stage research unit, laying off 120 staff. Three weeks later, Merck announced an additional $10bn in share buybacks.[28] Gilead may be moving in the same direction. The company's increases in research and development (from $2.1bn in 2013 to $3bn in 2015) pale in comparison to recent increases in share buybacks (see above).[21] A strategy of buybacks in the short term could threaten access to future innovations for patients in the long term.



## Public-private model out of balance

Some may argue that the trade-offs between innovation and access are the textbook result of private companies competing in free markets to maximise profits.[29] Yet governments protect pharmaceutical companies from truly free markets through patents, data exclusivities, and prohibition of drug reimportation.[30] Governments also invest in public goods such as basic science, technology development and start-ups, and medicines for vulnerable groups who could not otherwise afford them.[31] Though private investors should be rewarded for breakthrough advances, using these publicly granted privileges for access limiting prices and buybacks raises questions about whether the risks and rewards of innovation are being shared appropriately.[32]




**Gilead's key financial indicators ($bn) do not show any relation between profits and internal research and development investments. Gross profit is total revenue minus costs of goods sold. Announced share buybacks since January 2015 total $27bn. The 2015 figure shows executed buybacks and includes dividend of $1.9bn**

> The public is paying twice: for the crucial early investments in research and for high priced medicines

In the case of hepatitis C, publicly funded researchers in the US and Germany during the 1990s developed the subgenomic replicon, a research tool that overcame technical barriers to enable testing of antiviral compounds.[33 34] Apath, a university spin-off based in New York, commercialised the replicon with funding from the US National Institutes of Health's (NIH) small business and innovation research programme.[35] The replicon drew increased private investment into hepatitis C drug development, including from Pharmasset.[36 37] The laboratory from which Pharmasset emerged relied on funding from the NIH and the US Veterans Administration, and the start-up, like Apath, later received over $2m in NIH small business funding.[38 39]

Recently, however, an analysis of Gilead's tax returns indicated that the company had used a common industry practice to avoid nearly $10bn in US taxes by transferring the company's intellectual property for hepatitis C to an Irish subsidiary.[40]

Meanwhile, the public is paying twice: for the crucial early investments in research and for high priced medicines. The US Medicare programme for people over 65, for example, spent over $9bn on hepatitis C drugs in 2015, nearly 7% of its prescription drug budget.[41] The US Senate report also revealed that Medicaid spent over $1bn in 2014 while treating only 2.4% of its population with hepatitis C.[42]

These financial pressures have diminished the much touted public health potential of these medicines. Though treating patients in earlier stages (F0-F2 levels of fibrosis in the most common staging system) can reduce risks of disease progression and transmission,[43] the high prices have led many public systems across the US and Europe to treat only the sickest patients.[44 45]

## Search for future models

Mechanisms have been proposed to give health systems greater bargaining power to determine price and value.[49] Special approaches could be considered for breakthrough treatments for high prevalence and infectious diseases such as hepatitis C—for example, purchasing pools that bring together health systems to increase volume based discounts.[50] Another proposal would limit share buybacks to ensure prices and profits are linked to reinvestments rather than short term mandates determined by shareholders.[51 52]

What we ultimately need is innovation in innovation. Ignoring the consequences of prevailing organisations, systems, and financial imperatives in drug development will have costs for both current and future patients.

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