this week

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DOMINIC LIPINSKI/PA

Families affected by Primodos take their campaign to parliament in 2017, 30 years after the hormone pregnancy test was withdrawn from sale

Patients deserve NHS apology, says review

The government must immediately issue an apology "on behalf of the healthcare system" to women affected by three medical interventions—Primodos, sodium valproate, and pelvic mesh—and ensure they are listened to, supported, and compensated, a long awaited safety review has concluded.

"The system, and those that oversee it, need to acknowledge what has gone so badly wrong," said the report of the review, chaired by the life peer Julia Cumberlege. It came after years—decades in the case of sodium valproate and Primodos—of campaigning by patients and families.

The independent review was commissioned in 2018 by then health secretary for England, Jeremy Hunt, to assess use of the three medical interventions across the NHS. The report found that in all three instances patients' concerns were often dismissed and they had to fight to be heard. There were many occasions where regulatory bodies could have acted sooner and where poor communication with and between doctors prevented patients knowing about the risks.

Concerns were also raised regarding conflicts of interest, "both potential and real, in the provision of care or treatment, particularly where doctors have financial and other links with the pharmaceutical and medical device companies."

Primodos was a hormone pregnancy test taken by more than 1.5 million women for more than two decades before its withdrawal in 1978. It is claimed to have led to miscarriages and birth defects. Sodium valproate has been definitively linked to autism and learning disabilities in children when taken by their mothers during pregnancy to treat epilepsy. Pelvic mesh has been used to treat stress urinary incontinence and pelvic organ prolapse in women, many of whom have suffered badly from complications.

Cumberlege said, "I have conducted many reviews over the years, but I have never encountered anything like this: the intensity of suffering experienced by so many, and the fact they have endured it for decades. Much of this suffering was entirely avoidable, caused and compounded by failings in the health system itself."

The review team has instructed the government to appoint a patient safety commissioner to listen to patients, hold the system to account, and demand action. Separate schemes for the three medical interventions should also be established

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LATEST ONLINE

- Government unveils roadmap for making UK a "science superpower"
- Covid-19 delays publication of pharma funding declarations
- Coroners consider systemic failings in deaths of convicted breast surgeon's patients

SEVEN DAYS IN

New GP partners can now receive a "golden hello" of up to £20000

An incentive scheme offering new GP partners in England a one-off "golden hello" payment of up to £20 000 came into force this month.

From 1 July GPs can access up to £20 000 (if full time), a £4000 contribution towards overheads, and up to £3000 in a training fund for non-clinical partnership skills.

The deal was negotiated by the BMA and NHS England as part of a series of recruitment and retention initiatives, including boosting the numbers of GP partners. NHS England said the money was initially being made as a loan, but it envisaged that it would "automatically convert to a permanent payment after an expected minimum number of years (for example, five) as a partner."

To be eligible new partners must not have been a partner before; hold a profit sharing, legally liable partnership; commit to a five year partnership (or pay back a portion of the loan); and deliver at least two clinical sessions a week.

Richard Vautrey, chair of the BMA's GP committee, said, "This scheme shows faith in GPs and the partnership model—backed with additional investment—so that new partners can have the confidence in taking on this important role."

Gareth Iacobucci, *The BMJ* **Cite this as: *BMJ* 2020;370:m2665**

Covid-19

Outbreaks double in workplaces in England

Outbreaks of suspected covid-19 in workplaces in England almost doubled from 22 to 43 in the two weeks to 28 June, Public Health England reported. The figures showed that workplace transmission was trending up, while declining in most other settings. The government announced in May that people could return to work if unable to work at home. This has led to many construction sites, warehouses, restaurants, cafes, and, more recently, non-essential shops reopening.

Care home staff and residents get regular tests

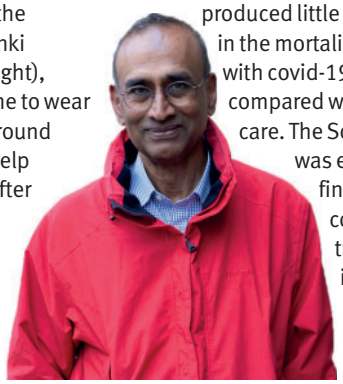
Care home staff in England will be tested for covid-19 every week, and residents every 28 days, the government said. Care homes looking after over 65s and people with dementia will be prioritised until testing is rolled out across all adult care homes next month. This move comes after a government study identified higher levels of the virus among care staff, particularly temporary staff who work in multiple settings and could pass on the virus to others if they are without symptoms.

RCP calls for flu vaccinations to be extended

The Royal College of Physicians called for this year's flu vaccination programme to be extended to include everyone over 50 to reduce the burden on the NHS this winter, provided there is enough stock. It added that flu vaccinations for NHS and social care staff should be brought forward, aiming for 100% uptake. Andrew Goddard, RCP president, said, "It is crucial that we learn the lessons from the last three months, as well as considering the additional challenges that future waves may bring if they coincide with winter flu."

Call for mandatory face coverings in public spaces

The president of the Royal Society, Venki Ramakrishnan (right), called for everyone to wear a face covering around other people to help tackle covid-19 after two reviews of the evidence. "The virus has not been eliminated, so as we lift lockdown and people increasingly interact with each other we need to use every tool we have to reduce the risk of a second wave of infection," he said. "There are no silver bullets but, alongside handwashing and physical distancing, we also need everyone to start wearing face coverings, particularly indoors in enclosed public spaces where physical distancing is often not possible." This should include shops and public transport, as is advised in several European countries.



Treatments are dropped from Solidarity trial

The World Health Organization accepted the recommendation from the Solidarity trial's international steering committee to discontinue the trial's hydroxychloroquine and lopinavir/ritonavir arms, as trial results showed that they produced little or no reduction in the mortality of inpatients with covid-19 when compared with standard care. The Solidarity trial was established to find an effective covid-19 treatment for inpatients.

Parliament

Peers to consider UK wellbeing after covid-19

The House of Lords' Covid-19 Committee called for evidence for its review of the pandemic's long term implications for the economic and societal wellbeing of the UK. The committee will begin by looking to the future and asking people for their views on the challenges to overcome and opportunities to do things better, especially in the light of systemic inequalities that the pandemic has highlighted in society. The deadline for evidence is Monday 31 August.

Substance misuse

England launches second phase of misuse review

The government launched the second part of its major review into the use of illegal drugs in England. The first part, commissioned by the Home Office, reported that drug deaths were at an all time high, that the market had become much more violent, and that drugs were costing society billions of pounds every year. The next stage will focus on treatment, recovery, and prevention and how people with substance misuse problems can turn around their lives. The final report is expected in December.

MEDICINE

The risk of serious illness from covid-19 is low for most children, says the RCPCH

Paediatrics

Most children no longer need to shield

The government asked specialists and GPs to contact families to discuss whether children still had to shield from covid-19, after evidence from the Royal College of Paediatrics and Child Health showed that the risk of serious illness was low for most children and that only those with the most severe conditions—such as cancer and immunodeficiency—should now be considered clinically extremely vulnerable. Children with asthma, diabetes, epilepsy, and kidney disease being cared for by their GP are unlikely to need to shield.

Head trauma cases surge during pandemic

Ten children with suspected abusive head trauma visited a specialist children's hospital from 23 March to 23 April, compared with a monthly average of 0.67 in 2017-19, doctors wrote in the *Archives of Disease in Childhood*. They also said that the figure was probably an underestimate. They concluded, "In the background of the intensely public SARS-CoV-2 pandemic, a more silent pandemic is occurring, of which the medical community must remain astutely aware."

Patient satisfaction

Concerns over discharge and home support

Most hospital inpatients were happy with the care they received and said their fundamental needs were met, in a survey from the Care Quality Commission. However, the survey of around 77 000 adults who had stayed in hospitals for at least a night last July found that 40% had left without written information about what they should or should not do after discharge, and 44% said they were not told about possible side effects of treatments. A third of frail people (33%) said the support they expected was not available after leaving hospital.

Pharma payout

Novartis pays $678m to settle fraud lawsuit

The drug giant Novartis agreed to pay $678m (£543m) to the US government to settle allegations that it offered doctors kickbacks to boost sales of its drugs. The government alleged that, under the guise of clinical education meetings, Novartis entertained high prescribing doctors at restaurants and night clubs. It was also accused of subsidising copayments of Medicare patients, an illegal tactic that generates more bills for the public payer. Two earlier settlements mean Novartis will pay nearly $1.3bn in total.

Food insecurity

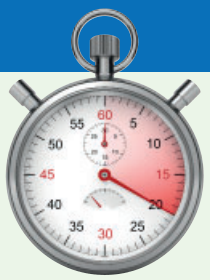
Inaction puts vulnerable children at risk

The government's lack of action in tackling food insecurity is condemning many children to a life of ill health, a House of Lords committee said. It recommended measuring how many people live with food insecurity and analysing why, as well as increasing pressure on industry to reduce sugar, salt, unhealthy fats, and calories in processed food.

Cite this as: *BMJ* 2020;370:m2693

SPAIN

Of 61 075 people tested for antibodies to covid-19 in the two weeks to 11 May **5%** tested positive. Seroprevalence was higher in Madrid **(13.6%)** than in coastal areas **(3%)** *[Lancet]*



SIXTY SECONDS ON . . . NHS CHARITIES TOGETHER

THAT NAME SOUNDS FAMILIAR

You may have heard of it as the organisation that received the £32m raised by Tom Moore (below). In total, £130m has been raised for the charity during the pandemic.

NICE! BUT WHO ARE THEY?

Formerly known as the Association of NHS Charities, it's essentially an umbrella organisation. Your local trust, for example, might have a charitable arm, and that could be a member of NHS Charities Together.

COULD BE?

Yes, well, membership isn't free. Depending on the income of the charity, annual membership costs between £1000 and £5000. NHS charities must be members to benefit from this covid-19 windfall.

THAT DOESN'T SEEM VERY CHARITABLE

Perhaps not, but NHS Charities Together says the fee contributes to running costs and member services. It also says that if a charity is eligible to join and applies for a covid-19 grant then its first two years of membership will be deducted from that grant, meaning it is not out of pocket.

BUT WHERE IS MY DONATION GOING?

Good question. There are 237 members, a rise from 140 when the covid-19 appeal was launched on 23 March. Each member charity has received an initial grant of £35 000.

AND THE REST?

A second wave of grants was awarded, based on £7 per staff member in the NHS trust that each charity supports. For example, £119 000 went to Southampton Hospitals Charity and £147 000 to Nottingham Hospitals Charity.

BUT WHAT'S IT PAYING FOR?

The money cannot be spent on direct patient care, so it buys things such as wellbeing boxes for staff and computer tablets that allow patients to speak to their relatives.

THERE MUST BE MONEY LEFT OVER?

So far, £20m has been distributed and £10m is available for charities to apply for by the end of August. The remainder will be available through further rounds of funding, so get in there quick—there's £100m to spend.

Abi Rimmer, *The BMJ*

Cite this as: *BMJ* 2020;370:m2681

(Continued from page 43)
to meet the cost of providing extra care and support to people who are eligible to claim. Additionally, regional networks of specialist centres (for mesh and pregnancy medications) should be established to provide care and advice.

The review also called for a "substantial revision" of the Medicines and Healthcare Products Regulatory Agency, "particularly in relation to adverse event reporting and medical device regulation." The MHRA should keep a register of all devices approved for the UK, and manufacturers should be required to apply to it before marketing devices. Devices should be approved after their risk, evidence base, and postmarketing surveillance plans have been assessed and have met the appropriate criteria.

"Pro-patients"

The vice chair of the review, the retired paediatric nephrologist Cyril Chantler, told *The BMJ*, "I don't want people to think this review is anti-doctor. It is pro-patients. The vast majority of doctors do the best to serve their patients, not least over the last three months."

Chantler said the review was about learning from the past, acknowledging and apologising for mistakes, and working to stop them happening again.

Other recommendations included that the GMC should have a list of financial and non-financial interests of all doctors, as well as doctors' clinical interests and specialties. A redress agency for people harmed by medicines and medical devices in future should also be established.

The review concludes, "If accepted, in principle, [the recommendations] now need to be implemented with a sense of urgency and real determination to stop future harm and provide care and support for those affected. We cannot stand by and let our recommendations gather dust."

Elisabeth Mahase, *The BMJ*

Cite this as: *BMJ* 2020;370:m2726

Covid-19's airborne spread is underestimated, warn experts

The virus can be transmitted by inhalation of microscopic droplets generated from breathing, talking, singing, and not just from coughing and sneezing
Don Milton, report author

Microscopic respiratory droplets generated by talking and breathing can hover in the air for minutes or hours and drift many metres before infecting people, argue 239 experts from 32 countries, in a commentary published in *Clinical Infectious Diseases*.

"We appeal to the medical community and to national and international bodies to recognise the potential for airborne spread of covid-19," wrote the scientists, who include physicians, epidemiologists, and environmental health experts.

"Studies by the signatories and other scientists have demonstrated beyond any reasonable doubt" that airborne droplets can pose a risk beyond 2 m from an infected person, the authors argued. They cited the case of a Chinese restaurant where video captured an evening in which the virus spread from table to table with no evidence of contact, direct or indirect, between the diners.

"By 'airborne' we mean that the virus can be transmitted by inhalation of microscopic droplets generated from breathing, talking, singing, and not just from coughing and sneezing," said Don Milton, professor of environmental health at the University of Maryland and one of the commentary's authors. "This does not mean that the virus can spread as easily over long distances as do measles or tuberculosis. Most transmission happens in closed, indoor spaces where there is poor ventilation and crowding, and people are close together and talking loudly or singing without masks."

Well ventilated

Researchers have been unable to grow coronavirus from aerosols in patients' hospital rooms, but these settings were unusually well ventilated, the commentary's authors contend.

Although the commentary does not single out any agencies, several of the signatories have lobbied the World Health Organization to recommend greater precautions against airborne transmission. WHO recommendations have prioritised hand washing and focused on the

A 10th of England's pandemic cases were in frontline health and social care staff

Health and social care staff, hospital patients, and care home residents made up a substantial proportion of covid-19 infections in England at the height of the pandemic, a report by Data Evaluation and Learning for Viral Epidemics (DELVE) says.

The multidisciplinary group of researchers convened by the Royal Society estimated that around 10% of all infections in England between 26 April and 7 June were in patient or resident facing workers (95% confidence interval 4% to 15%).

"We estimate that care providers had around four times the risk of infection as similar working age people in that period," said Guy Harling, a senior research fellow at University College London and a member of DELVE, at a briefing on 6 July. He pointed out that the figures represented only that six week period and that the covid-19 situation was rapidly changing.

At the pandemic's height hospital patients made up 11% of all covid-19 cases and care home residents a further 6%

At least 1% of all infections in England were definitely (started at least 14 days after admission) or probably (started at least seven days after admission) contracted by patients in hospital, the researchers found. "This is a substantial proportion of the cases in hospital as a whole," Harling said.

Data from the Covid-19 Clinical Information Network show that a rising proportion of cases were acquired in hospital between early March and early May, he added.

risk from coughed or sneezed droplets and infected surfaces. The *New York Times* spoke to several anonymous WHO consultants who praised the agency's overall effort but said that its infection prevention and control committee was bound by a rigid view of scientific evidence, was slow and risk averse in updating its guidance, and allowed a few conservative voices to drown out dissent.

WHO and the US Centers for Disease Control and Prevention recommended protection against aerosolised virus only during invasive medical procedures such as intubation. The commentary's signatories argue that agencies should be guided by the precautionary principle and should now recommend simple steps to counter potentially widespread aerosol transmission.

Some members of WHO's infection prevention and control committee have pointed to the opportunity cost if poorer countries are forced to redesign ventilation systems to counter a threat that is still not fully proved. Hospitals that recirculated air might need to install special filters and decontaminating UV bulbs, diverting resources from treatment.

But just opening windows could be the most effective measure, said Lidia Morawska, a professor in atmospheric sciences at the Queensland University of Technology and the organiser of the commentary.

"Opening windows to increase ventilation is the first thing to do," she told *The BMJ*. "What's most important is the recognition that we need good ventilation to remove the virus from the air."

Owen Dyer, Montreal

Cite this as: *BMJ* 2020;370:m2720

We estimate that care providers had around four times the risk of infection as similar working age people in that period

Guy Harling, DELVE

The report highlighted the factors implicated in the infection of staff, patients, and care home residents. These included inconsistent use of PPE; lack of access to testing; lack of physical distancing between staff and patients, in wards, corridors, and canteens; environmental and hygiene problems; difficulties in avoiding mixing infected and uninfected patients; rotation of staff; and inadequate surveillance systems to investigate individual infections and wider outbreaks.

The researchers called for "an ambitious and comprehensive approach" similar to the one that was used to combat meticillin resistant *Staphylococcus aureus*, but one that got results in months not years.

Anne Johnson, professor of infectious disease epidemiology at University College London and a DELVE member, said the report was "deliberately timed" to inform decisions around opening up of hospitals for non-covid-19 activities and to prepare for winter and any future waves of covid-19.

"This is a forward looking report with the idea that we must build resilience to infections within health and social care," she said.

Ingrid Torjesen, London

Cite this as: *BMJ* 2020;370:m2717

Ophthalmologists fined over price fixing for self-paying patients

The private hospital group Spire Healthcare and seven ophthalmologists have admitted taking part in an illegal price fixing agreement over the charges for an initial consultation for self-paying patients at a hospital in the north of England.

Spire was fined £1.2m and six of the consultants were fined amounts between £642 and £2978 after an investigation by the Competition and Markets Authority (CMA). The seventh, who blew the whistle on the deal, was not fined. The fines reflect a discount of 20%, applied because all the parties admitted the arrangement and cooperated with the investigation.

The agreement originated with a dinner organised by the management of Spire's Regency Hospital in Macclesfield (below), attended by five of the seven ophthalmologists, at which fees were discussed. After the dinner a Spire employee emailed the seven to suggest that an initial consultation be set at £200.

Three were already charging £200, and the other four agreed to raise their fees from £180. The CMA pointed out that entering an agreement to fix prices breaks the law, even if the prices are not subsequently changed. The arrangement lasted for nearly two years, from August 2017 to July 2019.

JOHN KEATES/ALAMY

Michael Grenfell, CMA's executive director of enforcement, said, "Initial consultations are an essential first step for people suffering from eye disorders. It is unacceptable that patients were unable to shop around and get the best deal because Spire and the consultants illegally set a minimum consultation fee.

"It is particularly disappointing that the CMA has had to take action in the private ophthalmology sector again, following a previous finding of anticompetitive practices in 2015. Today's decision and the subsequent fines send a clear signal that we will not tolerate anticompetitive behaviour."

Spire Healthcare said in a statement, "Spire Healthcare apologises for its conduct and fully cooperated with the CMA, agreeing to accept the CMA's findings in full and settle the case with a fine of £1.2m. The CMA acknowledged the group's strong compliance programme, which resulted in a reduction to the fine."

In 2015 the CMA fined CESP Limited, a membership organisation of 200 private consultant ophthalmologists, £382 500 after it admitted breaching competition law.

Clare Dyer, *The BMJ*

Cite this as: *BMJ* 2020;370:m2718

NEWS ANALYSIS

US purchase of world stocks of remdesivir risks sparking new "hunger games," warn observers

With Trump's nationalistic hoarding, **Jacqui Wise** looks at the implications for vaccines and treatments

The US has bought up almost all the world's supply of the antiviral drug remdesivir in a move that has important implications for access to medicines in the event of a more effective treatment or a vaccine against covid-19 becoming available.

The first 140 000 doses of remdesivir for covid-19 were supplied to trials around the world and have now been used. The US has bought more than 500 000 doses—all of Gilead's production for July and 90% of that for August and September.

The US has bought more than 500 000 doses of remdesivir—all of Gilead's production for July and 90% of that for August and September

Priti Krishtel, cofounder of the organisation I-Mak, which campaigns to increase access to drugs, told *The BMJ* that the move was just the beginning of the new "hunger games."

She said, "It signals that in the not so distant future all countries are going to be pitted against each other to get access to treatments and vaccines. High income countries and populations are poised to prevail at the direct expense of the poorest ones.

"Governments should not fall into this nationalism trap. If companies can't meet supply to meet global needs, governments absolutely should be overriding patents to any future treatments or vaccines to allow production by other suppliers. Anything less will result in countless deaths worldwide."

Ellen 't Hoen, a Dutch lawyer and head of Medicines Law and Policy, a group that works to ensure the availability of effective, safe, and affordable drugs for all, agreed. She told *The BMJ*, "I am not surprised. It is an extension of Trump's America First approach. It is similar to its attempts to get first access to Sanofi's covid-19 vaccine candidate. This is the new world where there is hand to hand combat over products and vaccines."

Unjustified price

Gilead has set a price for governments of developed countries of £390 for a vial of remdesivir, with a five day treatment course using six vials. In the US the price for private insurance companies will be $3120 per treatment course. The company's chairman, Daniel O'Day, said the price was set well below the value the drug provides to ensure equitable access at a time of urgent global need.

However, 't Hoen said, "The high price cannot be justified when you look at the cost of production, estimated to be less than a dollar a day, and the fact that the development of the covid-19 indication was largely carried out by the government."

Approval of remdesivir in the US and Europe was based on preliminary data published in the *New England Journal of Medicine*. This trial showed that remdesivir reduced the median time to recovery from 15 days to 11 when compared with placebo. This effect was not seen in patients with mild to moderate disease: time to recovery was five days in both the remdesivir group and the placebo group.

The trial was carried out by the US National Institute of Allergy and Infectious Diseases, and the advocacy organisation Public Citizen estimates that taxpayers contributed at least $70.5m to the drug's development.

"A lot of vaccines and drugs for covid-19 have benefited from public investment. Governments should make sure if they fund research they ensure fair pricing and global access," said 't Hoen.

"Marginal advantage"

Yannis Natsis, policy manager for universal access and affordable medicines at the European Public Health Alliance, told *The BMJ*, "These kinds of headlines fuel the competition between governments to secure access to a drug that appears to be of only marginal advantage. It pushes up the price that governments are prepared to pay."

Gilead, like other drug companies, is in talks with the European Commission and several European governments over its products. Natsis, who is also a board member of the European Medicines Agency, said, "The pharmaceutical industry is knocking on open doors at the moment and there is an astonishing lack of public scrutiny. We risk a much more dangerous and expensive repetition of the Tamiflu fiasco."

In the mid 2000s governments all over the world spent billions stockpiling antiviral drugs oseltamivir (Tamiflu) and zanamivir (Relenza), but a *BMJ* campaign for the release of clinical trial data on Tamiflu (bmj.com/tamiflu) showed the drug had little effect in managing or preventing flu.

Jonathan Van-Tam, England's deputy chief medical officer, told a parliamentary hearing that the UK has

High income countries and populations are poised to prevail at the direct expense of the poorest ones Priti Krishtel

It pushes up the price that governments are prepared to pay
Yannis Natsis

Potential difficulties securing future supplies
Jonathan Van-Tam

adequate supplies of remdesivir for emergency use, although he warned of potential difficulties securing future supplies. He said that brand new drugs to treat covid-19 were likely to be in "relatively short supply in the first instance" in comparison with existing generic ones such as dexamethasone.

Gilead has said that it is doing everything it can to accelerate manufacturing timelines and increase quantities of remdesivir to meet the growing demand around the world.

Compulsory licences

To tackle the remdesivir shortage, developed countries could issue compulsory licences to access generic versions. This is a provision in patent law and contained in article 31 of the international Agreement on Trade-Related Aspects of Intellectual Property Rights, whereby governments can decide to grant others the right to use the patent without consent of the patent holder. In the UK this is called crown use. Compulsory licensing is rare these days in high income countries but happened often during the HIV pandemic.

Gilead has licence agreements with manufacturers in India, Egypt, and Pakistan for the supply of remdesivir to 127 low and middle income countries, but that does not serve developed nations or countries outside these agreements. A Bangladeshi firm also produces a generic version but without a licence from Gilead, which it does not need as Bangladesh is classified as a least developed country

"Whether developed countries issue compulsory licences depends on whether they think the drug is important or not," said 't Hoen. "But considering there are so few treatment options for serious covid cases, many systems may want to have access."

Jacqui Wise, London

Cite this as: *BMJ* 2020;370:m2661

How does local covid-19 lockdown work, and will it be effective?

Just as England's national restrictions ease, Leicester's residents are advised to stay at home. Will it work—and will other cities follow?

What will local lockdown be in practice?

In Leicester's case, the city and the surrounding urban areas have shut non-essential retail and closed schools to all but vulnerable children and children of key workers. People have been advised to stay at home as much as possible and to maintain a physical distance of 2 m when outside. Local testing capacity has been increased.

The measures, to be reviewed after two weeks, will stay in place for as long as they are needed—although the relaxation criteria have not been made public.

Was it avoidable?

Yes, says the Independent Scientific Advisory Group for Emergencies (iSAGE), describing the situation as "both predictable and avoidable." It argues this lockdown is a consequence of lifting restrictions when the virus was still circulating widely, when there was "no functional system of find, test, trace, isolate, and support and when the prime minister was sending an implied message that things are 'back to normal.'"

In a statement iSAGE said the situation arose out of a failure to respond to the rise of infections before they reached crisis levels, adding, "This was a result of (a) an excessive centralisation and unavailability of data; (b) the fragmentation of the testing system; and (c) a lack of coordination with local authorities and with the NHS, PHE [Public Health England] and other agencies locally in understanding the cause, nature, and response to the outbreak. This has eroded trust in government and the information it provides."

The Department of Health has since agreed to share postcode level data on cases with local authorities.

iSAGE also warned that, considering Leicester's high levels of poverty, imposing lockdown without involving local authorities risks creating a "deep sense of resentment and of inequity."

What triggers an alert?

No criteria have been made public. PHE has released its preliminary investigation into Leicester, but it does not provide much clarity. It reported that the "strongest evidence of an outbreak" was that, unlike other Midland areas, a rising proportion of new infections were in children and working age people. It found "no explanatory outbreaks in care homes, hospitals, or industrial processes to immediately explain the apparent rise," noting the evidence for the scale of the outbreak was "limited and may, in part, be artefactually related to growth in availability of testing."

Will it work?

"We know widespread lockdowns work, and what remains to be seen is how a local one will in the UK," said Keith Neal, emeritus professor of the epidemiology of infectious diseases at the University of Nottingham. "With a high level of compliance, cases should begin to fall in one to two weeks, although increased testing could also mask what is a real decline in new infections."

Will others follow?

Many other areas in England are reportedly being monitored. PHE data on 2 July showed the weekly number of cases per 100 000 population varied widely, from 0.31 (in Lambeth, south London) to 141.32

ALEX HANNAM/EMPICS/PA

(Leicester). The next highest areas were Bradford (45.8), Barnsley (35.1), Rochdale (35), and Oldham (30.1).

In Scotland, because of a spike in cases in parts of Dumfries and Galloway—which borders England—the lockdown rules that were due to be eased will remain.

Neil Ferguson, a former covid-19 adviser to the government, said it was "inevitable" more areas would be locked down. Speaking to the BBC on 1 July, he said, "We're relaxing lockdown rules, and that means contacts in the populations are going up. In some places we'll get clusters of transmissions. What's critically important is that we detect those early and adopt measures necessary to reduce transmissions again."

Elisabeth Mahase, *The BMJ*

Cite this as: *BMJ* 2020;370:m2679

EDITORIAL

Lessons from Leicester: a covid-19 testing system that's not fit for purpose

England's chaotic test and trace programme cost lives in the Midlands city and must be reformed

With the flare-up of covid-19 and re-imposition of lockdown, the population of Leicester is suffering the fallout of a chaotic testing system that seems to have forgotten its prime purpose—namely to trigger prompt, targeted measures, informed by local knowledge and up-to-date surveillance. Without swift and decisive action by those at local and national levels who understand communicable disease control, England will see further lockdowns and more avoidable deaths.

Leicester was a city at risk, with high levels of social deprivation and ethnic diversity. We now know that cases spiked in late May and that new cases were being detected throughout June at rates of over 100 per 100 000 population per week. But these data were made available to the local authority only days before lockdown was re-imposed on 30 June[1] and were not made public for several days after that. In Germany the rates required to trigger local lockdown are 35-50 cases per 100 000 per week,[2] supported by a well functioning, locally based track and trace system.

Delays and diversions

Why did the local authority teams not have the data they needed to detect the outbreak and take swift action? In May, England's chief medical officer apologised to directors of public health for the lack of data from the so called pillar 2 system, which relies on private laboratories for testing in the community. General practitioners had been promised these data weeks before.[3] It now seems clear that Public Health England (PHE) was itself receiving delayed, poor quality, and incomplete data from the private laboratories. Test results have been reaching PHE via a tortuous route encompassing the National Pathology Exchange and NHS Digital and often lack basic essential details such as NHS number and postcode.[4]

Poor contracting seems partly to blame. Covid-19 was classed as a notifiable disease on 6 March, placing clear legal obligations on medical practitioners and laboratories for prompt reporting of all cases to PHE,[5] whether diagnosed or suspected. But this reporting obligation was not included in the contract with at least one of the private companies.[6] These contracts seem to have focused on doing as many tests as possible, rather than establishing testing as a key component of a system designed to contain the virus and save lives.

If a ministerial directive blocked timely data sharing, the minister should be held accountable

Central government may also have caused delays. Up-to-date local data were available to PHE's rapid investigation team[7] but were not shared with local authority teams, apparently on the orders of a government minister.[8] It is hard to see what could justify such a prohibition. Local authorities have statutory public health duties and crucial local knowledge.[9] Data sharing agreements have now been signed, but if a ministerial directive blocked timely data sharing, the minister should be held accountable for avoidable deaths and the consequences of reinforced lockdown. There could be a substantive legal case to answer.

PHE seems paralysed and divorced from the field of action. Its main response to data showing increasing incidence in Leicester was to increase test numbers rather than to initiate

Outside gyms in Leicester were out of bounds just as they were being reopened in the rest of England

MIKE EDGERTON/PA

ALEX HANNAM/EMPICS/PA

JOE GIDDENS/PA

effective control measures—inaction that is all the more culpable given the city's population make up.

Getting it right

PHE is now, since 1 July, publishing data at local authority level, but only after mounting pressure and the prime minister's claim in parliament that data from both the NHS (PHE) and private testing systems "are shared with all authorities across the country." Wales has been doing this all along. Detailed data at postcode level are now being shared with local teams in England, but there are continuing concerns about quality and completeness (J DeGruchy, personal communication, 2020).

Many questions demand answers. How can new cases of a notifiable disease not be reported promptly to all those responsible for communicable disease control at a local level? In what way is England sufficiently different from Wales to justify such a crucial difference in reporting? Who decided, and on what basis, not to make disaggregated testing data available to local teams? Why should test results from a privately contracted laboratory be treated differently from those from NHS and PHE laboratories? And what is the plan for how to control spread in the other hotspots?

England's testing system stands in stark contrast to Scotland, which decided early on to build on existing capacity in local public health boards and ensure that tracing was locally led. Scotland has pursued a "zero covid" policy to drive down the number of cases through a test, trace, and isolate strategy, with daily reports on the Scottish government website of how many people were tested, how many tested positive, and other key indicators such as deaths and hospital admissions. This transparent approach is based on a clear strategy, underpinned by clear lines of accountability. Confirmed daily new cases are in the single digits and have consistently declined over the past few months.

In the early days of the HIV epidemic understandable constraints were placed on how much detail about infections could be put into the public domain, on grounds of stigma, confidentiality, and very small numbers. With covid-19, precisely the opposite applies. Knowing how many covid-19 cases have been found in a locality will allow people to calibrate their response. As in the BSE crisis, the government's paternalistic, centralising tendency has meant that efforts to control the spread of the virus have been overwhelmed by a lack of trust not just in individuals to make their own decisions, but in local professionals and teams.[10] This chaotic system has been established by a government with little understanding of communicable disease control. The announcement of a further £5bn for contracts to provide covid-19 testing[11] offers little hope for a change in direction.

Independent SAGE has called for an enhanced local response in Leicester, rooted in additional support for the affected population.[12] Nationally, action is needed now if we are to avoid further damaging lockdowns. We need transparent and timely sharing of data, proper investment in local public health infrastructure, no more standalone testing systems,[13] a fully functioning "find, test, trace, isolate, and support" system as set out by Independent SAGE,[14] and a new determination to reduce levels of circulating virus, if we are to avoid the 30 000 additional deaths by next April implied by England's chief medical officer.[15]

Leicester's city centre was once more deserted and non-essential shops closed as local lockdown was reimposed on 30 June

Mike Gill, former regional director of public health, London, UK
M Gill mgilm1@gmail.com
Devi Sridhar, professor of global public health, University of Edinburgh
Fiona Godlee, editor in chief, *The BMJ*

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THE BIG PICTURE

The faces of NHS resilience and courage

As an expression of thanks and respect the acclaimed photographer Rankin has created a collection of 12 portraits of health workers to mark the NHS's 72nd anniversary.

Among his sitters was Farzana Hussain, a GP in Newham, east London, pictured here as her portrait was unveiled at Piccadilly Circus. "It's difficult to put into words how privileged I feel to be able to go to work every day and to help battle this global pandemic," she said.

"Every member of staff has their own story, fears, and hopes. I think Rankin's photography brings this out really well."

Rankin, who more usually photographs subjects such as the Queen and the Rolling Stones, said, "I was moved by the incredible efforts of people across the NHS. I hope these images portray the resilience and courage they show every day in the face of real adversity."

The portraits also include an intensive care consultant, a psychiatrist, nurses, a midwife, porter, cleaner, paramedic, pharmacist, 111 call centre worker, and an information officer and have been donated to the NHS.

Alison Shepherd, *The BMJ*

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DOMINIC LIPINSKI/PA

EDITORIAL

Coronavirus: patient and public involvement

Absent in the early stages of the pandemic, it must now move centre stage

The covid-19 pandemic saw statutory policy commitments to patient and public involvement and shared decision making in health systems abandoned, the "nothing about us without us" mantra left hanging in the breeze.

Decisions had to be made fast, but policy makers' choice of expert advisers excluded those with expertise rooted in lived experience—patients, families, and frontline health and social care professionals. This was regrettable.

Patient and civil society advocacy groups may have lacked seats on expert committees but took the lead in providing information, advice, and support for their communities.[3] They have lobbied for a voice in policy making,[4] for a focus on inequalities,[5] and for policies to take account of the reality of people's lives.[6] They have also accumulated a wealth of information from the patient community on the physical, mental, social, and economic effects of the pandemic,[7 8] effects that highlight the urgency of restoring essential medical services[9] and the need for a comprehensive public health response.[10]

Embedding the patient voice

The precipitate loss of civil liberties and continued uncertainty around the efficacy of policies that profoundly affect how people live and work have eroded trust and prompt searching questions.

First, why were the voices of patients and the public tuned out? Despite decades of activism, public and patient involvement is still largely seen as "nice to have" but non-essential—a second step to be carried out after an initial round of consultation with academic, clinical, public health, and policy experts.

Second, how could health leaders do better now? Patient advocates, organisations, and civil society networks are primed to inform joint learning from the pandemic and help shape post-covid services and research agendas.[12-14] New collaborations are under way,[15 16] but more are needed. Regrettably, the explosion of research into covid-19 has been associated with a drop in public and patient involvement,[17] but a joint initiative to agree core outcomes has been launched (www.covid-19-cos.org/).

Experienced advocates should be appointed to advance shared decision making at strategic levels

Third, how can we ensure that patient and public involvement becomes irreversibly embedded in decision making? Approaches vary and most are flawed. The voluntary advisory groups attached to general practices and hospital departments in the UK (whose work was immediately suspended at the pandemic's onset) are unrepresentative and too often used to "rubber stamp" policy decided elsewhere. Industrial quantities of patient experience data are rarely used for quality improvement.[18] Co-design of services is still uncommon and co-production of research not widely achieved.

New approaches are needed that capitalise on online communication—now the norm for patient and civil society groups. Input from under-represented groups is not hard to achieve, if the will is there and digital divides addressed.[19] More collaborative platforms should be established to unite patient communities with professional groups, informed by successful existing models (www.parkinsonnet.com/).[20]

Mutual respect

Mutual understanding and respect is essential in any partnership, and patient leadership must be taken seriously by both health professionals and patients. Experienced advocates should be appointed to advance shared decision making at strategic levels in the health sector. More and better training programmes in patient leadership are required for managers, clinicians,[21] patients, and carers,[22] along with wider uptake up of joint care models in which patients and carers are integrated into multidisciplinary teams in both primary and secondary care.[23 24]

Collectively, these steps will help change healthcare culture and counter what Montori describes as a "corruption in the mission" of health systems.[25]

Finally, providing people with full online access to personal health records and test results will improve the quality and safety of care and raise health literacy on both sides of the professional fence. This is essential as remote services increase and people take on a larger role in self-monitoring and self-management. Patient and public involvement should be routine in medical education, with health professionals taught and appraised in partnership skills.[26]

Covid-19 has precipitated a global health crisis, plunged the world into economic recession, put the spotlight on structural inequalities, including racism, and galvanised the call for action on climate change. The knowledge to confront these challenges needs to be co-produced.[27] Patient and public involvement must be taken seriously, embedded robustly, and never sidelined again.

Tessa Richards, senior editor/patient partnership
trichards@bmj.com

Henry Scowcroft, patient editor, *The BMJ*, London
On behalf of *The BMJ*'s international patient and public advisory panel

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EDITORIAL

Dexamethasone in the management of covid-19

Preliminary trial results are mostly good news, but timing is everything

On 16 June, investigators on the covid-19 RECOVERY trial revealed in a press release[1] that 2104 participants with severe covid-19 given 6 mg dexamethasone once daily had an 8-26% lower mortality than 4321 participants given standard care. Changes in the NHS covid-19 treatment protocol were soon announced based on these results. The results remain neither peer reviewed nor published, although a preprint is available.[2]

RECOVERY is the first large randomised trial to test immunosuppression as a therapeutic option in covid-19. It is important to note that tempering a maturing immune response to the SARS-CoV-2 virus is different from having underlying immunosuppression at the time of infection.

Pathogenesis

The pathogenesis of SARS-CoV-2 differs fundamentally from that of its predecessors SARS-CoV-1 and MERS, for which poor outcomes correlate with viraemia and high viral loads in the lung at time of death.[6-8]

Guidance from the US Centers for Disease Prevention and Control (CDC)[9] recommends against corticosteroid therapy in coronavirus infections because steroids "prolonged viral replication" in patients with MERS. Unlike the MERS coronavirus, however, SARS-CoV-2 is rarely found in blood during the symptomatic phase of covid-19, even in people with severe disease.[11] Furthermore, hypoxaemia may develop just as the viral load in the upper respiratory tract is falling rapidly or becoming undetectable.[12 13]

Patients admitted to hospital with covid-19 typically report symptom onset three to five days after exposure (fatigue, chills). Transition to severe disease with hypoxaemia occurs five to seven days into the symptomatic illness. In the RECOVERY trial, dexamethasone was beneficial for participants treated seven or more days into the symptomatic phase, with the onset of hypoxaemia. Importantly, there was a non-significant trend (P=0.14) towards possible harm affecting participants without hypoxaemia and not on mechanical ventilation. RECOVERY findings therefore support use of dexamethasone only for patients with hypoxaemia, not those with milder disease. The data do not support use of dexamethasone or other corticosteroids in the outpatient setting.

LEWIS HOUGHTON/SPL

It would not be reasonable to delay use of a widely available treatment with a demonstrated mortality benefit

Corticosteroids such as dexamethasone have broad effects on innate and adaptive immunity. Adaptive immunity may be integral to covid-19 immunopathology, as the onset of acute respiratory distress syndrome correlates temporally with the appearance of a specific antibody against SARS-CoV-2.[14] In March, a retrospective study from China reported that, in the subset of patients who progressed to ARDS, objectively sicker patients who received methylprednisolone had lower mortality rates than patients not receiving methylprednisolone.[15] In RECOVERY, corticosteroid therapy increased 28 day survival in patients developing acute respiratory distress syndrome. Despite concerns about the possibility of steroid associated complications, it would not be reasonable to delay use of a widely available treatment with a demonstrated mortality benefit.

Evidence gaps

Unresolved questions remain, however. RECOVERY investigators did not explore optimal type of corticosteroid nor timing, dose, or duration of treatment. The dose of dexamethasone used was roughly half the functional corticosteroid dose used to prevent treatment induced acute respiratory distress syndrome in moderate or severe pneumocystis pneumonia. It is not yet clear whether corticosteroids are the best option for all patients in the second phase of covid -19 or whether treatment may be less beneficial for some subsets, such as people with diabetes. Ongoing trials of immune modulation with calcineurin inhibitors may shed light on these questions.

Adults requiring ventilation in RECOVERY were relatively young, with a mean age of 59 years. The benefits and risks of dexamethasone for the oldest adults remain unclear. Virological measures such as viral load were not reported and would be helpful in future studies as they may help to guide treatment decisions, including timing. Longer term follow-up of the original cohort will be critical to identify harms associated with corticosteroid use.

The RECOVERY investigators and collaborators should be congratulated for organising and completing this trial during a pandemic. Perhaps less desirable, is the now common practice of communicating clinical trial data early through press releases. Clinicians and policy makers need access to detailed data and analyses before making or accepting therapeutic decisions or recommendations.

Raymond M Johnson, associate professor of medicine and of microbial pathogenesis Raymond.Johnson@yale.edu

Joseph M Vinetz, professor of medicine, Yale School of Medicine New Haven, Connecticut

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COVID-19

The inside story of the RECOVERY trial

The UK's flagship covid-19 clinical study, involving more than 3500 researchers, has been hailed worldwide—but some say it is far from perfect. **Jacqui Wise** and **Rebecca Coombes** unpick criticisms around a vital cog in the pandemic response

On 16 June the world heard that the first proven lifesaving treatment for covid-19 had been found. Dexamethasone, a widely and cheaply available steroid, was reported to have cut deaths by a third among hospital patients with covid-19 who needed ventilation and by a fifth among patients receiving oxygen only. In the chaotic, fear filled first half of 2020, this was at last an evidence based treatment from a randomised controlled trial, showcasing what the collective strengths of the NHS could achieve.

Conducted by researchers at Oxford University, the ongoing Randomised Evaluation of Covid-19 Therapy (RECOVERY) trial involves all major hospitals in the UK on an unprecedented scale and as many as 3500 doctors, nurses, and research staff, including consultants, junior doctors, and those newly graduated. Within its first three months it reported its first policy changing result: that the widely promoted antimalarial drug hydroxychloroquine was ineffective.

Scientists are concerned about transparency and a worrying trend for announcing trial results by press release

This was swiftly followed by the dexamethasone announcement, seen by many as a much needed ray of hope among the gloom of spiralling infections and deaths.

"The UK has really delivered here," says Martin Landray, deputy chief investigator of RECOVERY. "It involves hospitals from Truro to the Western Isles, Northern Ireland across to King's Lynn. The patients have been fabulous: they were ill, frightened, alone, and elderly. The success is down to amazing teamwork across the clinical community and the incredible support of patients and their families."

But global recognition and headlines also bring intense scrutiny. Alongside international praise RECOVERY has drawn criticisms from scientists about transparency and a worrying trend for announcing trial results by press release and without the underlying data.

RECOVERY trial timeline

10 March	Trial protocol is drafted
11 March	WHO declares the covid-19 outbreak a pandemic
19 March	First RECOVERY patient is recruited
23 March	UK goes into lockdown
14 May	10 000th RECOVERY patient is recruited
5 June	Alerted by its data monitoring committee, the trial halts the hydroxychloroquine arm, concluding that the drug has no clinical benefit for patients in hospital with covid-19
9 June	Trial's statistical analysis plan is published
16 June	Results of the dexamethasone arm announced by press release
22 June	Dexamethasone preprint published on medRxiv
29 June	Results of lopinavir-ritonavir arm indicate no clinical benefit in hospital patients with covid-19

It had to be easy for the clinician, in PPE and in a pressurised situation
Martin Landray, RECOVERY

Press release or peer review?

When the dexamethasone result was announced on 16 June it came unexpectedly early and not in a research paper but from a media announcement. The UK government told NHS hospitals to act immediately, even though the data had not yet been published in full as either a preprint or in a peer reviewed journal; it was a week later that a preprint appeared on the medRxiv preprint server.

Scientists are worried about the lack of public scrutiny of the data before major policy decisions were made, particularly given the retractions of high profile papers in journals such as the *Lancet* and *New England Journal of Medicine* just weeks earlier. The arm of RECOVERY evaluating hydroxychloroquine was ended earlier in June after the Medicines and Healthcare Products Agency (MHRA) asked the investigators to review the data early, prompted by the *Lancet* retraction. Their analysis concluded that the drug conferred no meaningful mortality benefit in the treatment of covid-19, leading to the trial's first announcement of results, although again this was done through the media. At the time of writing the full data have still not been published.

"I think it is irresponsible to release the results only in a press release; a press release is not evidence," says Tobias Kurth, professor of epidemiology and public health at the Charité Berlin University of Medicine and one of *The BMJ*'s statistical advisers. "This habit has to stop now. Even though we are in a difficult situation and urgently need to find something that works, it is important to show all the methods and data."

Landray's defence is that the results were so stark that they had to be publicised, especially in the case of

The trial's hydroxychloroquine dosage

The high doses of hydroxychloroquine used in RECOVERY—800 mg at 0 and 6 hours followed by 400 mg at 12 hours and then every 12 hours for up to nine additional days—have raised concern among experts.

David Jayne, professor of clinical autoimmunity at Cambridge University, said that current recommended doses for rheumatologic disease are typically 300-400 mg/day and that the maximum dose for malaria has been 800 mg in the first 24 hours. "The reasons behind the dose selection in the RECOVERY trial are unclear," he says. "Hydroxychloroquine overdose is associated with cardiovascular, neurological, and other toxicities, occurring with doses over 1500 mg, and higher doses are associated with fatality." He is concerned that hydroxychloroquine toxicity may have contributed to the adverse outcomes and that conclusions based on these results may be unreliable.

Martin Landray, RECOVERY's deputy chief investigator, says, "We did not choose these doses by accident. The dose comes from modelling by Nick White, professor of tropical medicine at the University of Oxford, and his team, who have extensive experience with this drug. They developed detailed pharmacokinetic models, considering the best way in which to rapidly achieve drug levels that might be high enough to kill the virus but not so high as to trigger toxicity. Their work has recently been published as a preprint on medRxiv."

Leading the research on the ward

When it comes to conducting urgent lifesaving research, watching videos on the internet isn't what normally springs to mind.

"When you do research trials, certainly for industry ones, there's masses of e-learning to do, and it is really offputting," says Ray Sheridan, consultant physician at the Royal Devon and Exeter trust, where 49 patients were recruited to RECOVERY. "A lot of it is really pointless, but RECOVERY's was very doable and just had a 5-10 minute video to watch for each section."

Sheridan says the protocol was very straightforward. "We set up 24/7 access to research nurses, but often enough I did the randomisation myself, it was so straightforward. We used web based data entry forms that took you a matter of minutes to enter someone into the trial."

All patients had to be have been admitted to hospital to qualify, but participation was not limited to just those in intensive care. "In a lot of trials, if you are 90 and have dementia you don't go into routine trials, whereas these were all comers," says Sheridan.

Staff had plenty of time to discuss the trial with potential participants, despite the emergency nature of their infection. "There was never any pressure on patients to go into the trial, and often they wanted to talk to their families as well," says Sheridan, who is also involved in neurodegenerative disorder trials, where "people want a lot more time to think about it."

For those there is a 20-30% uptake, but with RECOVERY almost everyone they spoke to wanted to do it. Sheridan says, "We were absolutely clear that we didn't know whether these drugs worked and that this is the only way we can find out if they do. This was quite brave of patients, as one of the arms was standard care, but this didn't put them off."

Sheridan says his clinicians felt in complete control, having had long discussions about the pros and cons of the various drugs tested before finally deciding to help test all of them. "There were a lot of reservations about the steroid arm, and some of the data coming through suggested the HIV drug wasn't working, based on one or two studies in China, although those patients were recruited after 11 days of being in hospital whereas we were looking from day 1. The fact that we went into all arms, open without the prejudices, felt good to me. If we'd been really clear that we didn't like one arm, that would have been uncomfortable."

We turned the wards into a positive place
Ray Sheridan, consultant physician

Sheridan adds, "We went into this pandemic with a real sense of doom and gloom. We were really expecting to be like Italy, but we felt we turned the wards into a positive place. Patients were coming in terrified. But we were running research trials and were offering our patients the best possible options, and that helped overall."

dexamethasone, as it was the first evidence of a treatment that reduces mortality in patients with covid-19.

What happened between the subgroups in the dexamethasone trial was very unusual, he says. "There was a very clear benefit, especially for patients on ventilators. This was a pre-specified analysis with a highly statistically significant difference between the patients depending on the level of respiratory support they were receiving at the start of the study. Importantly, we saw no benefit (and the possibility of harm) among patients not requiring any form of respiratory support.

"If you look at Brazil, Mexico, or India, with thousands of patients dying every week, there will be many patients on ventilators who will suit [this] treatment," Landray told *The BMJ*, adding that his team spent a week making sure the results were robust. They then shared their findings with "senior leaders in international healthcare," who made it clear that the group had to take action.

"We had a choice: do we wait for full publication or make information available to the world to make their own decision? If we hadn't released the [results], people would have said we sat on it," he says.

Trial by design

Landray emphasises that to put the trial in context it's important to remember the sense of impending doom felt by clinicians in the UK back in March.

"Covid-19 is a disease that affects huge numbers and where case fatality is high," he says. "More than one in four patients in hospital die, and of those admitted to intensive care units the prospect is worse. Back in early March none of us were sure if we were going to run out of ventilators or healthcare staff. Doctors in Italy were using words such as war zone." The priority, he says, was to find a treatment that would reduce deaths—and ideally one where doctors could access a few thousand courses rapidly.

As the pandemic broke, the World Health Organization and the European Medicines Agency emphasised the need for large randomised trials with

a control group rather than many small and inconclusive studies, as had come out of previous epidemics.

Landray and his colleagues wanted to embed research into standard clinical care and took inspiration from the large simple trials of the 1980s, in particular the International Studies of Infarct Survival (ISIS), randomised controlled trials of treatments for acute myocardial infarction. "It had to be easy for the clinician on the ground, in PPE and in a pressurised situation, and a minimal burden for the patient," says Landray. "Many academic and commercial trials have accumulated so much extra baggage over the years, such as long case report forms and 10 page patient consent forms."

To Ray Sheridan, a consultant physician at the Royal Devon and Exeter NHS Foundation Trust, which recruited 49 patients to RECOVERY, it seemed as though the NHS was "turning the engines on big time.

"You had 176 hospitals, and you could see the recruitment numbers going up astonishingly," he says. "There was an unprecedented level of interest. I'd say 95% of patients were delighted there was a trial going on in their local hospital and felt like they were 'doing their bit' by being involved."

The mammoth task of mounting a large scale trial amid the first major pandemic in 100 years was accomplished in record time. Landray and fellow chief investigator Peter Horby drafted the protocol on 10 March, and the results for the dexamethasone arm were announced just 98 days later, after more than 11 000 patients had been enrolled into the trial.

Patients enrolled in the open label RECOVERY trial are randomised to standard care or to one of six treatment arms: hydroxychloroquine (now ended), dexamethasone (also ended), lopinavir-ritonavir, azithromycin, convalescent plasma, and, in a second randomisation for patients who deteriorate, the anti-inflammatory drug tocilizumab.

For Ray Sheridan, the trial meant that clinicians didn't have to make snap decisions on emerging treatments. There was a lot of pressure to use hydroxychloroquine and azithromycin in combination, partly because there was emerging evidence from France, he says. "But it was non-randomised, and many of those patients weren't on oxygen, and a lot weren't in hospital for very long." Sheridan thought these were nothing more than pilot data, yet the study had begun to inform decision making about the pandemic.

"The RECOVERY trial stopped patients getting these treatments, and this was a relief," says Sheridan, "Otherwise, a lot of patients would be given steroids by some consultants, hydroxychloroquine by others, and ultimately we wouldn't be learning anything."

But for clinical pharmacologist John Warren, formerly of the MHRA, the RECOVERY approach to drug selection was too random. He says the approach seems "like a roulette wheel—here's an antiviral, let's try it."

Landray says the trial's choice of drugs was influenced by the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG), an expert committee of the Department of Health, and a WHO prioritisation process that took place in early 2020. The selection was ultimately governed by four principles: Is there a reason to believe the drug will work (for example, on the basis of laboratory test results or of experience from other viral infections)? Is the safety profile understood? Is the drug available in enough quantities to allow it to be tested in a trial of several thousand people? And, if the treatment is successful, can it be rapidly scaled up?

Other commentators have questioned the absence of the promising antiviral remdesivir in RECOVERY. The drug is currently being given to selected patients through the government's Early Access to Medicines Scheme after early trial data showed that it shortened time to recovery. *The BMJ* understands the lack of a remdesivir arm is because its manufacturer, Gilead, said it could offer only a limited supply of the drug and the investigators turned it down.

To this Landray would comment only that "we just couldn't get the supply we needed." But he added, "This is a global effort, and SOLIDARITY [a large multi-country WHO trial] is studying remdesivir in sufficient quantities. We don't want to repeat their effort. This is not competitive, and there was a reason to say, 'This is being done elsewhere, let's leave them to it.'"

Transparency in ACCORD

The taskforce will be led by Jonathan Van-Tam, England's deputy chief medical officer

RECOVERY isn't the only covid-19 trial or research platform facing questions about transparency.

On 29 April England's health and social care secretary, Matt Hancock, announced the Accelerating Covid-19 Research and Development (ACCORD) programme, which will look at potential drugs that could be fast tracked through early stage clinical trials. If they show promise they would then be fed into large scale studies such as RECOVERY.

The drugs so far confirmed are MEDI3506 (an anti-IL-33 monoclonal antibody), zilucoplan (a complement C5 inhibitor that could block severe inflammatory responses), bemcentinib (an AXL inhibitor, with early data showing it can reduce viral infection and lung inflammation and block the SARS-CoV-2 spike protein), and acalabrutinib (a Bruton's tyrosine kinase (BTK) inhibitor developed for severe lung inflammation).

The decisions on which drugs are included in ACCORD are made by a "therapeutics taskforce," but its membership is not listed anywhere accessible, and there are no published terms of reference or published minutes. A spokesperson for the Department of Health and Social Care said that the taskforce is being led by the deputy chief medical officer for England, Jonathan Van-Tam, but would not confirm any other members.

The spokesperson said, "The taskforce does not choose the drugs that go to trial as these are recommended by the prioritisation panel. The panel includes over 20 contributors, including frontline NHS clinicians, academics with expertise in covid-19 disease mechanisms, and relevant expertise from the life sciences sector. The current membership of the taskforce is under review, and we will publish the full list, alongside the members of the prioritisation panel, when this is completed."

ACCORD reports to the business secretary, Alok Sharma. The DHSC's website states that it is a partnership between the Government Scientific Office, the NIHR, the clinical research company IQVIA, and the drug company AstraZeneca. The BMJ understands that one of the members of the taskforce is Mene Pangalos, executive vice president of biopharmaceuticals R&D at AstraZeneca. Of the five drugs publicly released in the current ACCORD trial, two are AstraZeneca compounds: interleukin 33 (IL-33) and alcabrutinib.

There are concerns that the taskforce is influenced by the industry and acting as the conduit for political direction of clinical research. The clinical pharmacologist John Warren told The BMJ that the taskforce should include a medicinal chemist, pharmacologist, pharmacokineticist, virologist, immunologist, and toxicologist.

Competition for patients

At the start of the pandemic researchers were told to halt all non-covid-19 research and focus efforts on potential covid treatments, Landray says. The National Institute for Health Research (NIHR) says that there is a highly expedited process to approve applications and that a great many have been submitted. Researchers report that it can take weeks or months to get a decision. "The process is centralised and bureaucratic," says Beverley Hunt, medical director of the charity Thrombosis UK and a practising clinician. "And we don't know who is reviewing these proposals. There is huge frustration felt by many academics."

Hunt was, like others treating covid-19 patients with pneumonia, seeing high rates of hospital associated thromboembolism and other forms of thrombosis and thought that a good trial was urgently needed to compare different doses of anticoagulants. A consortium of UK thrombosis experts submitted a research proposal to the NIHR in April but were told it was a low priority area.

Hunt told *The BMJ*, "The problem was they had a preconceived view of what works and only wanted to look at antivirals and anti-inflammatories, and the problem of thrombosis was not obvious at the start of the pandemic in the UK." Eventually, after much discussion, an anticoagulation arm was added to the REMAP-CAP trial (involving patients with community acquired pneumonia being treated in intensive care).

The NIHR says that since March it has prioritised 48 public health research studies, out of more than 400 that have been assessed.

In contrast, RECOVERY gained momentum during the spring. For Landray, an important difference between RECOVERY and many other studies is when the study began: at the start of the pandemic, not in June, when patient numbers were falling off. The trial was aided by what Landray calls "fabulous" efforts by the NIHR's clinical research networks to cut red tape. Meanwhile, academics involved in smaller trials were getting frustrated at what they saw as an overtly bureaucratic process to give the green light to vital research.

James Galloway, a consultant rheumatologist at King's College Hospital in London and an investigator on a smaller trial called TACTIC, is impressed by the speed at which RECOVERY was set up: "Basically, hospitals could quickly switch on and deliver it." However, he has concerns about the sample size calculation, essentially seeking as many patients as possible. "For example, did we really need 1800 patients in the hydroxychloroquine arm to find out it didn't work? Could we have found this out sooner? That's 1800 patients who didn't go into other RECOVERY trial arms or even different studies." (He acknowledges that he has a personal bias as an investigator on a different trial.)

Landray says it is important to remember that RECOVERY is a "platform trial," looking at several drugs at the same time. "We knew we needed compelling evidence that a drug worked or didn't work, and so it was necessary that the trial was sufficiently powered. In the context of a disease that kills tens of thousands of people, a reduction in mortality of one fifth would have major implications—for example, it is the difference between 20 000 deaths and 16 000 deaths. That is 4000 deaths prevented."

The approach seems like a roulette wheel—here's an antiviral, let's try it
John Warren, clinical pharmacologist

They had a preconceived idea of what works
Beverley Hunt, Thrombosis UK

He adds, "Covid-19 is not a rare disease, so the overall impact of such modest treatment effects is massive. To be able to detect or dismiss such an effect requires a large trial. For example, a study with 2000 patients in the active arm and 4000 in the control arm would give 90% power at P=0.01 to detect a risk reduction of about one fifth."

The trial is so large that it recruited around 15% of all patients with covid-19 in UK hospitals, though Landray points out that of course this means 85% of such patients are not in the trial. Some patients would not have wanted to enter a trial, others may not have been approached, and some may not have been suitable for some reason. At some hospitals up to 80% of covid patients were recruited, while in others it was as low as 3%.

The trial's legacy

For many involved in RECOVERY, the longer term issue is how the trial can reset the way clinical trials are conducted in the future. Landray says, "How can we build on the involvement of patients and clinicians and the timely access to relevant data? We now need to apply the lessons from this approach to other major health challenges such as heart disease, cancer, arthritis, and mental health."

Sheridan is keen to keep up the momentum. "We have seen things done in a really streamlined, efficient way, and people really want to hold on to that. We liked the fact that it was really pragmatic, so the moment you know a drug is not working it gets dropped and then other drugs can get added. It also shows that you can use the whole of the NHS rather than just the main academic centres.

"You have a whole lot of people in hospitals who are not usually involved in research on a day to day basis who really want to carry on."

Jacqui Wise, freelance journalist, London
Rebecca Coombes, head of news and views, *The BMJ* rcoombes@bmj.com

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Main covid-19 drug trials in UK

ACCORD—A clinical trial platform to assess candidate agents that runs in alliance with a national collaboration of phase 2 drug development platforms (www.accord-trial.org)

CATALYST—A trial to test the anti-inflammatory drug infliximab, currently used to treat rheumatoid arthritis and inflammatory bowel syndrome

PRINCIPLE—A platform trial of interventions in older people carried out in primary care (www.phctrials.ox.ac.uk/principle-trial)

RECOVERY—A platform trial evaluating existing or new drugs in patients being treated in hospital (www.recoverytrial.net)

REMAP-CAP—A platform trial for critically ill patients (www.remapcap.org)

TACTIC—A trial to test baricitinib, a drug used to treat rheumatoid arthritis, and the monoclonal antibody ravulizumab (https://cctu.org.uk/portfolio/COVID-19/TACTIC)