Institution: King's College London		
Unit of Assessment: 21 Sociology		
Title of case study: Better medicines regulation for patient and public health		
Period when the underpinning research was undertaken: 2001 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Dr Courtney Davis	Reader in Global Health and Social Medicine	From January 2013
Period when the claimed impact occurred: 2014 - 2019		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Effective regulation and technological assessment of new medicines are key to ensuring that drugs are safe and effective for patients, and cost-effective for health systems. Research from King's College London has shown how regulatory developments in the US and EU have allowed new drugs to enter the market on the basis of less robust clinical evidence, which in turn may undermine appropriate clinical decision-making, patient safety and the ability of policy makers to determine the value of new therapeutics for health systems and population health.

This research has (i) influenced World Health Organization (WHO) policy on new cancer drugs, including criteria for the inclusion of these drugs in its Essential Medicines List; (ii) strengthened the capacity of civil society organisations to scrutinise and advocate for enhanced medicines policy within the EU and internationally; and (iii) informed and empowered patient activists in the UK.

2. Underpinning research

Paradoxically, during a period in which decision-makers have expressed a commitment to evidence-based medicine and policy, a dominant trend in the United States and the European Union over the past 30 years has been to lower evidence standards for, and 'fast-track' an increasing number of new therapies onto the market despite significant uncertainty around their benefits and risks. For example, in 2018, 48 of 59 (81%) new drugs approved by the US Food and Drug Administration (FDA) benefited from some kind of regulatory pathway allowing for expedited testing or regulatory review. In both the US and EU, these special regulatory programmes most commonly benefit high-cost cancer drugs.

Proponents claim these initiatives incentivise medical innovation and speed patient access to promising therapies, and that critical data on drug efficacy and safety (which would normally be required before drugs enter the market) can be generated in the post-market period while drugs are being prescribed to patients. However, health policymakers, clinicians and patients depend on the availability of reliable evidence to determine whether the benefits of new and more costly medicines will outweigh their harms and offer meaningful improvements over older, cheaper drugs.

An on-going programme of research by Dr Courtney Davis – supported by competitively-awarded grants from the Economic and Social Research Council (ESRC), the Wellcome Trust, and the European Commission's Consumers, Health, Agriculture and Food Executive Agency (CHAFEA) – explores the drivers and implications of these trends.

Investigating new paradigms in US and EU medicines policy

Between 2001 and 2012 Davis and colleagues undertook the first EU-US comparative analysis of the drivers, implementation and impacts of new 'fast track' policies for regulating innovative pharmaceuticals [1]. Through in-depth, case study analyses of regulatory decision-making in those regions over a twenty-year period, King's research showed the new policies did not necessarily lead to the prioritisation, incentivisation or approval of therapeutically important medicines. On the

contrary, in each case examined, regulators had approved onto the market drugs of marginal or highly uncertain benefit. Some of those drugs posed unacceptable risks to patients and were subsequently withdrawn. Drawing on these findings, Davis's 2016 *BMJ* paper [2] considered the implications and potential dangers of proposals by the European Medicines Agency (EMA) to further loosen regulatory standards by expanding the pathways through which companies could market new drugs on the basis of immature evidence. The paper noted that the proposals had been subject to minimal scrutiny and called for a more public and inclusive debate.

Exploring the implications of current regulatory policy for cancer care

Davis's most recent research has focused on the regulation of new cancer drugs, which now comprise the single largest category of new drug approvals in Europe and the US. Davis's research shows that although uptake of new cancer medicines is often accompanied by steep prices, and high expectations, evidence at their point of approval rarely supports claims to 'breakthrough' status [3,4,5]. For example, a retrospective cohort analysis by King's researchers of all cancer drugs approved by the EMA between 2009 and 2013 [3] showed that the majority lacked evidence that they extend patients' survival or improve quality of life. Where survival or quality of life gains *were* demonstrated, they were marginal according to established thresholds. Critically, King's research [6] also showed that adequate evidence to address knowledge deficits is rarely demanded by FDA or EMA in the post-market period, undermining claims that clinical uncertainty at time of market approval will be resolved through evidence generation once drugs are being prescribed to patients. The research recommended that regulators raise standards of drug approval by requiring that new drugs demonstrate clinically meaningful gains in survival and quality of life at the time of their approval.

King's researchers also undertook the first systematic analysis of the health and budgetary impacts of the UK's NHS Cancer Drugs Fund (CDF) – a ring-fenced fund set up to enable patients to access high-cost cancer therapies [4]. The research highlighted the problems of setting a low threshold for reimbursement by demonstrating the limited clinical benefits associated with these drugs and concluded that the CDF had failed to provide meaningful benefit to patients or society, recommending the avoidance of similar 'ring-fenced' drug access funds in other countries. Critically, the research suggested that the GBP968,000,000 spent on the CDF resulted in overall net harm to population health since it displaced other, more cost-effective treatments. Moreover, unrealistic expectations in relation to the clinical benefits offered by new drugs may actually harm individual patients if these expectations result in aggressive and inappropriate treatment with toxic chemotherapies towards the end of life [5].

3. References to the research

[1] Davis, C., & Abraham, J. (2013). *Unhealthy Pharmaceutical Regulation: Innovation, Politics and Promissory Science*. Palgrave Macmillan, New York.

[2] Davis, C., Lexchin, J., Jefferson, T., Gøtzsche, P., & McKee, M. (2016). "Adaptive pathways" to drug authorisation: adapting to industry? *British Medical Journal*, 354, i4437. DOI:10.1136/bmj.i4437

[3] Davis, C., Naci, H., Gurpinar, E., Poplavska, E., Pinto, A., & Aggarwal, A. (2017). Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. *British Medical Journal,* 359, j4530. DOI:10.1136/bmj.j4530.

[4] Aggarwal, A., Fojo, T., Chamberlain, C., Davis, C., & Sullivan, R. (2017). Do patient access schemes for high-cost cancer drugs deliver value to society? Lessons from the NHS Cancer Drugs Fund. *Journal of the European Society for Medical Oncology*, 28(8), 1738-1750. DOI:10.1093/annonc/mdx110.

[5] Davis C. (2014). Drugs, cancer and end-of-life care: A case study of pharmaceuticalization? *Social Science & Medicine*, 131, 207-214. DOI:10.1016/j.socscimed.2014.12.007c.

[6] Salcher-Konrad, M., Naci, H., & Davis, C. (2020). Approval of cancer drugs with uncertain therapeutic value: A comparison of regulatory decisions in Europe and the United States. *Millbank Quarterly*, 98(4), 1219-1256. DOI: 10.1111/1468-0009.12476

4. Details of the impact

As spending on expensive new medicines increasingly displaces other treatments, and policies modelled on the 'fast-track' initiatives of the FDA and the EMA are adopted by drug regulatory agencies across the globe, careful evaluation of these initiatives, and transparent, inclusive debate has become ever more important. Through engagement with, and dissemination to regulators, international governmental bodies, clinicians, politicians and civil society groups at national and supranational levels, research led by Davis has influenced policy and practice in a variety of ways.

Influencing World Health Organization (WHO) policy on new cancer drugs

According to expert advisors sitting on the WHO's Essential Medicines Committee for Cancer, Davis's research [3,4] *"has been pivotal in drawing attention to the often marginal and uncertain benefits offered by many new cancer drugs relative to their price"* [A] and has shaped WHO policy with respect to eligibility criteria for cancer medicines proposed for the WHO's Essential Medicines List, and WHO policy and recommendations around affordability and access to cancer medicines.

In March 2018, the WHO convened the Essential Medicines List Cancer Medicines Working Group (EML-CMWG) to advise on criteria for the selection of cancer drugs for WHO's Essential Medicines List, a list of the most efficacious, safe and cost-effective medicines for priority conditions. Drawing on King's research, which challenges the increasing tendency of regulators to approve new cancer drugs without evidence of clinically relevant impacts on patient survival or quality of life [3; B p.7-8], the EML-CMWG advised on *"the need to have overall survival as the main eligibility criterion of a medicine proposed for EML listing"* [B p.4]. This recommendation was subsequently endorsed by the WHO Expert Committee on Selection and Use of Essential Medicines [C p.xvi]. As noted by members of the WHO Essential Medicines Committee for Cancer; *"Dr Davis' seminal publications in this area provided crucial underpinning policy research that shaped the recommendations and conclusions of the working groups & subsequent WHO policy around inclusion (and exclusion) criteria for inclusion of cancer medicines on the Essential Medicines List"* [A]. In 2019 the EML was updated, adding 12 cancer medicines, purposefully selected due to their designation as 'best in terms of survival rates'. As noted by the WHO Director-General Dr Tedros Adhanom Ghebreyesus *"around the world, more than 150 countries use WHO's Essential Medicines List to guide decisions about which medicines represent the best value for money, based on evidence and health impact. The inclusion in this list of some of the newest and most advanced cancer drugs is a strong statement that everyone deserves access to these life-saving medicines, not just those who can afford them"* [D].

Davis's research [3,4] also informed WHO recommendations related to the pricing and reimbursement of new cancer drugs. In 2017, the World Health Assembly requested guidance from WHO on options to enhance the affordability and accessibility of new cancer medicines. In response, the WHO convened an expert advisory group to report on the pricing of cancer medicines and its impacts. The resulting report drew extensively on King's research [E, p.11, 20, 35, 67, 106], including the finding that the UK Cancer Drugs Fund *"failed to deliver meaningful value to patients and society*" [E, p.67]. As a result, the recommendations resulting from the report advised that countries should *"[a]void the use or establishment of funds earmarked for the provision of cancer medicines"* [E, p.106].

Building capacity of civil society organisations to scrutinise and advocate for enhanced medicines policy within the EU and internationally

Through collaboration and engagement with advocacy groups and consumer health organisations, Davis's research [1,2,3] has also facilitated a more transparent and inclusive discussion on medicines policy internationally. Her research, and subsequent dissemination activities, have strengthened the capacity of such groups to engage in high-level discussions with policymaking and regulatory bodies, improving effective scrutiny and better enabling them to pursue favourable outcomes. [text removed for publication]

The International Conference of Drug Regulatory Authorities (ICDRA) provides drug regulatory authorities of WHO Member States with a forum to meet and discuss ways to strengthen collaboration. The ICDRAs have been instrumental in guiding regulatory authorities, WHO and interested stakeholders, and in determining priorities for action in national and international regulation of medicines. In 2016 an international coalition of patient groups and NGOs (including

AIDS Treatment Action Campaign South Africa; the Global TB Community Advisory Board International; SECTION27 South Africa; Health Gap International; and Treatment Action Group US/International) drew on Davis's BMJ analysis piece [2] to petition national medicines agencies and governments attending the ICDRA to stop lowering regulatory standards [G]. With Davis's research, the coalition of five patient groups and NGOs concerned with the regulation of medicines in the public interest, both in their various countries and globally were able to create more succinct arguments based on evidence. In particular their petition directly referenced Davis's research and stated that *"the lowering of regulatory standards must be stopped… the public interest requires that medicines must be proven to be safe, effective and of high quality before allowed onto the market"* [G].

Similarly, key European consumer health organisations, including BEUC (the European umbrella organisation for Consumer Associations), EPHA (the European Public Health Alliance), the Medicines in Europe Forum, Test Achats (the Belgian Consumers' Association), and Health Action International Europe have drawn on Davis's research to develop evidence-based policy recommendations and advocate for stronger medicines regulation in their interactions with the public health community, the European Medicines Agency, the European Commission and politicians at European and member state level.

For example, at a national level, the NGOs Test Achats, Stand Up for Cancer, and Doctors of the World used findings from Davis's research [3] to develop their knowledge and understanding of the marginal or uncertain benefits offered by some new anti-cancer drugs [H1]. As a result, the group developed ten key recommendations on the accessibility and affordability of medical treatments at a symposium with members of the Belgian House of Representatives on 8 November 2018 [H2]. Recommendation 3 cited Davis's research [3] to argue that price should be proportionate to the health gains offered by new therapies [H3, p.29]. This recommendation was supported by the majority of Belgian political parties [H2].

At the level of the supranational EU: *"the evidence provided by Dr Davis and her colleagues has helped civil society groups like BEUC make a stronger case for the need to reinforce the EU medicines approval system, and to engage with the EMA and EU policymakers with a more authoritative voice. BEUC's advocacy efforts in the last years have resulted in increased awareness among EU policymakers about the need to continue strengthening the regulatory framework, so it can provide more value to patients and consumers"* [I].

Informing and empowering patient activists in the UK

Davis's engagement and educational activities with patient activists in the UK have enabled advocates to engage more effectively in their work with politicians and decision-makers. [text removed for publication].

5. Sources to corroborate the impact

[A] Testimonial from members of the WHO's Essential Medicines Committee for Cancer.

[B] WHO (2018) EML Cancer Medicines Working Group 2018, Report of the meeting 22-23 March 2018.

[C] WHO (2019) The Selection and Use of Essential Medicines: Report of the 22nd WHO Expert Committee. WHO Technical Report Series, No. 1021, 2019.

[D] WHO (9 July 2019) WHO updates global guidance on medicines and diagnostic tests to address health challenges, prioritize highly effective therapeutics, and improve affordable access. [press release]

[E] WHO (2018) Pricing of cancer medicines and its impacts: a comprehensive technical report for the World Health Assembly Resolution 70.12, 2018.

[F] [text removed for publication]

[G] Report of a petition by AIDS Treatment Action Campaign (S. Africa), the Global TB Community Advisory Board (International), SECTION27 (S. Africa), Health Gap (International) and Treatment Action Group (US/International) (2016).

[H] Documents corroborating change in the Belgian House of Representatives: [H1] presentation slides (slide 14), [H2] online summary of Symposium, [H3] full report of the Symposium and recommendations.

[I] Testimonial from Senior Health Policy Officer, BEUC (The European Consumer Organisation).