Breakthrough drugs and institutional corruption. The case sofosbuvir-based treatments in England

Piotr Ozieranski[1], Donald Light[2], Lawrence King[3]

[1] – Department of Social and Policy Sciences, University of Bath, Claverton Down, Bath, UK; Lecturer

[2] – School of Osteopathic Medicine, University of Medicine and Dentistry of New Jersey, USA; Professor

[3] – Department of Sociology, University of Cambridge, Free School Lane, Cambridge, UK Professor of Sociology and Political Economy Department of Sociology Cambridge UK

Corresponding author: Piotr Ozieranski, p.ozieranski@bath.ac.uk

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Contributors and sources
Donald Light is Professor of Comparative Healthcare at Rowan School of Osteopathic Medicine. DL assisted on data analysis, concept development and writing. Lawrence King is Professor of Sociology and Political Economy at the Department of Sociology, University of Cambridge. LK conducted interviews, analysed the data, assisted on writing and led the research project reported in this paper. Piotr Ozieranski is Lecturer at the Department of Social and Policy Sciences, University of Bath. PO conceived and drafted the paper, conducted ethnographic observations and analysed the data.

Piotr Ozieranski is the guarantor of the article.

The paper draws on 25 of Gilead's internal documents disclosed following a US Senate investigation, 32 purposively sampled interviews with UK based stakeholders, 150 NICE and NHS England policy documents, observations at five policy events discussing HCV treatments, and stakeholder financial disclosures

Transparency declaration
The guarantor (Piotr Ozieranski) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Details of ethics approval
The study presented in this article received ethical approval from the Research Ethics Committee at the Department of Sociology, University of Cambridge in April 2015.

Box with key messages:

- Gilead lobbied key decision-makers directly and indirectly - via encirclement of other parts of government, funding of Clinical Policy Leaders, patient advocacy groups and "umbrella organisations."
- Gilead demonstrated a new intensity in well-established lobbying tactics by investing unparalleled resources in building relationships with Clinical Policy Leaders, an inner circle of clinicians involved in taking policy decisions, and patient advocates.
- Gilead championed a new source of third-party party support – multi-stakeholder "umbrella organisations" developing policy proposals and generating public health evidence
- The breadth and intensity of Gilead's lobbying generated the risk of institutional corruption - undermining the standards of trustworthy drug evaluation through the introduction of commercial bias

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Standfirst:

- The breadth of Gilead's lobbying risked compromising trustworthy drug evaluation

Pharmaceutical companies have been criticised for using lobbying to push for drugs that provide limited clinical gains,[1] are not cost-effective,[2 3] have cheaper alternatives,[4 5] or target problems not require pharmacotherapy.[6] It would seem unlikely, however, that truly innovative drugs would require any lobbying. Contrary to this expectation, our research into Gilead's two breakthrough hepatitis C virus (HCV) treatments – sofosbuvir and ledipasvir-sofosbuvir – demonstrates a new level of intensive lobbying targeting NICE, NHS England, the Department of Health and other parts of government. Taken altogether, these lobbying tactics created risks of "institutional corruption", understood as deviation from the established standards of trustworthy drug evaluation.[7]

Our analysis draws on Gilead's internal documents disclosed following a US Senate investigation,[8] 32 purposively sampled interviews with UK based stakeholders, 150 NICE and NHS England policy documents, observations at five policy events discussing HCV treatments, and stakeholder financial disclosures.

Thin evidence for approval and reimbursement

Introduced to the NHS in England in 2014-15 (Table 1), Sofosbuvir-based treatments created unprecedented policy challenges, including the need to reconcile their

breakthrough clinical characteristics, cost-effectiveness, affordability considerations and gaps in the evidence base.

[Table 1]

With some clinical trials showing sustained virologic response rates above 90%[9 10] sofosbuvir was the first direct acting antiviral (DAA) licensed in viral genotypes 1-6 (together with peginterferon or ribavirin),[11] while ledipasvir-sofosbuvir was the first all-oral regimen approved in genotype 1.[12] For Gilead, the clinical value of its treatments justified aggressive pricing,[13] with the list price of £34,983 for sofosbuvir and £25,987 for ledipasvir-sofosbuvir.[14 15] Considering a long-term perspective, NICE recognised that the two drugs were cost-effective as they fell below its cost-effectiveness threshold of £20,000-30,000 per QUALY in most indications.[14 15] Nevertheless, their short-term budget impact raises affordability concerns, as there are 160,000 diagnosed HCV sufferers.[16 17] The cost of reimbursing sofosbuvir-based treatments (and, to a lesser extent, other DAAs) has increased rapidly. While the Early Access Programme (EAP) for patients with advanced liver disease cost £18.7 million the subsequent commissioning policy for patients with cirrhosis became NHS England's largest investment in new treatments in 2015, costing £190 million.[18 19]

Importantly, the clinical evidence base behind sofosbuvir-treatments was surprisingly thin. For example, consistent with criticisms formulated by the Oregon Center for Evidence-Based Policy[20], the NICE Evidence Review Group in the sofosbuvir appraisal noted,

> "Direct evidence of sofosbuvir versus comparators is lacking and in most cases efficacy data come from single arms of a variety of RCTs (or non-RCTs)"[21]

These policy challenges should be addressed by objective and transparent drug appraisal and reimbursement involving independent experts and officials prioritising patient and taxpayer interests and norms of scientific good practice. This trustworthy policy process was undermined by Gilead's broad set of lobbying tactics generating risks of institutional corruption.

Direct lobbying of key decision-makers

The interviewed industry representatives argued that Gilead focused on "direct lobbying", understood as communicating in its own name with key decision-makers in the appraisal and reimbursement process: NHS England, responsible for designing the EAP and commissioning policy, and the Department of Health, responsible for the tender of different DAA therapies to be included in the commissioning policy. This lobbying tactic, referred to as "negotiations", is traditionally used by industry in the drug approval process.[22] [23] Our interviews conceded, however, that direct lobbying was not highly effective, primarily because government officials suspect the motives of companies regarding the price of sofosbuvir-based treatments. A company representative expounded,

> "Gilead (…) don't get a huge amount of access from the Department of Health. (…) (…) So not everything that is in the interests of Gilead is detrimental to NHS England and the Department of Health but sometimes when you are trying to interact with them it feels like they assume that it is."[24]

Given these challenges Gilead exercised pressure on the key decision-making bodies through other stakeholders – termed "influencers"[25] – in the policy process. These "indirect" lobbying tactics were characterised by low transparency and risked introducing commercial bias to the stakeholders' agendas.

Encirclement lobbying of other parts of government

A new form of lobbying used by Gilead involved exercising pressure to parts of government driving pharmaceutical industry investment in the life sciences sector, most notably the Office of Life Sciences.[26] A company representative noted,

> "[Gilead communicated] (…) some of the broader implications [of decisions on its drugs]: (…) what is this going to do for innovation, what is this going to do for the principle of people developing treatments that cure? Gilead had a couple of meetings with George Freeman MP [Minister for Life Sciences] so they are communicating that kind of level."[24]

Enclosure lobbying was crucial in opposing NHS England's attempts to contain the budget impact of sofosbuvir-based treatments. While Gilead unsuccessfully challenged NHS England's request to NICE introducing a three-month delay implementing NICE guidance of sofosbuvir,[27] [28] Gilead successfully opposed NHS England trying to include affordability as a consideration in the sofosbuvir-ledipasvir appraisal.[29] [30] In both instances, Gilead's argument was that altering existing appraisal rules could drive away its investment. A company representative recounted,

> "Gilead (…) will make representations to anybody that they believe has (…) influence (…) because that is important strategically. (…) Otherwise they [Gilead] can't make long-term investments [in the UK]."[31]

Funding Clinical Policy Leaders

The US launch of sofosbuvir involved Gilead using senior clinicians as "Key Opinion Leaders"[32] (KOLs) to influence other drug prescribers and shape clinical guidelines.[33] In the UK, Gilead went further, seeking to "[d]evelop KOL champions" as possible "trustworthy advocates" for sofosbuvir during the NICE appraisals and the development of reimbursement policy by NHS England.[34] These, however, are far more than KOLs traditionally used by the industry[32] as Gilead funded an inner circle of Clinical Policy Leaders (CPLs) affecting national decisions.

While the interviewed clinicians saw themselves as impartial and genuinely acting in patients' interest, this perception may underestimate the impact of tacit forms of co-optation based on financial ties and shared research activity.[35] To document this, and in the absence of relevant expert conflict of interest (COI) declarations published by NICE or NHS England, we examined the relationship between experts in appraisal and reimbursement of sofosbuvir-based therapies and Gilead as well as 39 other pharmaceutical sector companies using 386 scholarly outputs published from January 2014 to March 2016, and information on drug company websites.

More than half of these 41 experts had industry ties, resulting in 409 potential COIs (Table 2). The experts had about equal numbers of COIs with Gilead and its main

competitors, AbbVie, Bristol-Myers-Squibb and Janssen.[36] However, Gilead was the company with ties to the largest number of experts (16 out of 23).

[Table 2]

Industry ties were reported by about half of the experts (16 out of 33) comprising two Clinical Reference Groups (CRGs) advising NHS England, almost all experts (7 out of 8) contributing the NICE appraisals of sofosbuvir-based therapies, and all experts involved in designing the EAP (3 out of 3) (Table 3). Likewise, those leading on the EAP had the highest numbers of potential COIs (average = 51.7 COIs per expert), followed by the NICE clinical consultees (average = 17.8) and the CRG members (average = 6.7). The number of potential COIs with Gilead and its competitors was similar in each expert category.

[Table 3]

Gilead's "strong relationships"[34] with these 41 CPLs is found in a second body of evidence, the number of research projects with industry, public (e.g. research councils) and third-sector funding (e.g. charities) (Table 4). More than half the research published by the clinical experts (59 out of 114 projects) was industry-funded. Among individual sources of funding, Gilead funded the largest number of projects (22) and clinicians (15). Reliance on Gilead as a key source of funding was consistent throughout all expert categories in the appraisal and reimbursement process but was particularly notable for experts contributing to the design of the EAP and to the NICE appraisals.

[Table 4]

These estimates of industry-clinician relationships are conservative as we found no outputs for 5 experts, and COIs were reported only regarding the subject of specific outputs. Further, not all industry-funded research is published or listed on company websites.

It is concerning that the voice of clinical experts – often with links to Gilead – was critical for addressing major areas of uncertainty in Gilead's NICE submission. For example, the Appraisal Committee relied on expert input in recommending the use of sofosbuvir in treatment-experienced patients with HCV genotypes 1, 4, 5 and 6, for which Gilead did not provide any clinical trial evidence.[14]

Facilitating patient and umbrella group advocacy

The US launch of sofosbuvir emphasised using patient advocacy groups as part of disease awareness campaigns targeting HCV sufferers. In the UK, following earlier industry practices using patient advocates as "third parties" in NICE appraisals, [37] [38] Gilead viewed engagement with local patient groups[25] as "[c]ritical to addressing the reimbursement landscape"[34] by influencing NICE and NHS England.

Financial reports submitted to the Charity Commission by patient organisation and charity consultees in the sofosbuvir and sofosbuvir-ledipasvir appraisals demonstrate rapidly increasing funding from Gilead. For example, coinciding with the early stages of the sofosbuvir appraisal and directly preceding the EAP (Figure 1), its donations jumped by almost 314% in the financial year 2014. Further, consistent with the clinical research funding pattern, over a six-year period Gilead became the company most connected to the NICE consultees via financial ties (Table 5).

[Figure 1]

[Table 5]

Gilead enhanced the influence of patient advocates by helping to create or fund third party, multi-stakeholder "umbrella organisations" as a new form of insider influence.[34] They were exemplified by the London Joint Working Group on Substance Use and Hepatitis C and the Hepatitis C Coalition. Their members included many of the clinical and patient organisation that consult in the NICE appraisals and members of NHS England CRGs. The two organisations were funded by Gilead (and other companies) and supported by consultancies listing Gilead as its client.[39 40 41 42] Gilead also probably led the establishment of the Hepatitis C Coalition.[25 43]

As part of third-party lobbying, the two groups were vital for helping Gilead generate policy positions and public health evidence supporting its negotiations with NHS England.[25] As usual, the interviewed stakeholders stressed their independence from Gilead, but the company benefitted from their excellent access to decision-makers. A pharmaceutical company representative described a patient organisation's role as a broker between Gilead and NHS England during negotiations over the commissioning policy.

> "Gilead were trying to get a meeting with NHS England (…) and eventually there was a Parliamentary event (…) and at that event [Gilead] spoke and James Palmer

> from NHS England spoke and between [Gilead] and the patient group they persuaded James Palmer that it was worth having a conversation with Gilead."[24]

However, the perception of Gilead's influence diminished the trustworthiness of one of the umbrella groups' policy proposals on establishing a clinical infrastructure for DAAs. A representative of one of the groups noted,

> "[Gilead's] influence on the Improvement Framework gave NHS England an excuse to hold up the framework. [At] NHS England and just generally there was an uncomfortable feeling that it was just one company who set up this group."[43]

Breakthrough pharmaceutical lobbying

The extent of Gilead's lobbying of England's key decision-making bodies was beyond anything found in the United States, posing significant risks of institutional corruption.[7]. The company deployed well-established forms of influence – direct communication with key decision-makers and using patient advocates as third-party champions of its treatments. In addition, Gilead elaborated KOL influence by building relationships with CPLs involved in developing policies on its treatments. New tactics also included encirclement lobbying via other parts of government and using "umbrella groups" as a new type of third party producing public health evidence and policy proposals. The company took these influence tactics to new limits by investing unparalleled resources in funding CPL research and patient group advocacy. Ironically, Gilead's lobbying tactics resembled the pharmaceutical lobbying playbook from Poland, a postcommunist country that has long suffered from excessive industry influence.[44] While measuring the exact impact of Gilead's lobbying is impossible, it clearly exacerbated risks posed by the

debatable evidence supporting its treatments,[45] increased the already uneven policy playing field,[46 47] with possible detrimental effects on public health and budgets.[48]

Tables

Table 1 Timeline of licensing and appraisal of sofosbuvir and ledipasvir-sofosbuvir

	Licensing (European Medicines Agency)		Appraisal (NICE)		NHS England Early Access Programme		NHS England Cirrhosis Policy	
	Start	Finish	Start	Finish	Start	Finish	Start	Finish
Sofosbuvir	Apr-13	Jan-14	Jun-13	Feb-15				
Sofosbuvir-ledipasvir	Feb-14	Nov-14	Mar-14	Nov-15	Apr-14	Mar-15	Jun-15	N/A

Note. We established the dates included in the table based on information provided on NICE and European Medicines Agency websites

Quarters Sociological Calendar 1971 Quarters by policies

Table 2 Potential conflicts of interest (COIs) of clinical experts involved in the appraisal and reimbursement of sofosbuvir-based therapies

	AbbVie	Bristol-Myers-Squibb	Gilead	Janssen	Number of COIs with pharmaceutical industry	Number of experts with COIs with pharmaceutical industry (% of all experts)
Grant and research funding	4	6	12	6	72	17 (41%)
Advisory boards	7	8	8	12	97	15 (37%)
Dissemination	7	7	8	10	79	13 (32%)
Consultancy and review	7	8	7	9	87	12 (29%)
Payments	4	6	5	5	51	9 (22%)
Work and ownership	1	2	3	3	23	4 (10%)
Total number of COIs	30	37	43	45	409	-
Total number of experts with COIs (% of all experts)	8 (20%)	9 (22%)	16 (39%)	14 (34%)	-	23 (56%)

Note. The list of clinical experts included in the analysis comprises 33 members of NHS England's Hepatobilliary and Pancreas and Infectious Diseases Clinical Reference Groups advising NHS England on the reimbursement of sofosbuvir,[49 50 51 52] three experts involved in designing the Early Access Programme[53] and eight experts contributing to the NICE appraisals of sofosbuvir and ledipasvir-sofosbuvir.[14 15] There were 41 experts in total, with three experts contributing to the appraisal and reimbursement of sofosbuvir-based treatments in two roles. From 7th to 20th March 2016 we conducted PubMed and Embase searches, identifying 386 outputs, including published papers and conference abstracts, with 373 listing 36 of the 41 clinical exerts as authors. Out of these outputs, 267

had potential conflict of interest (COI) declarations, with 135 mentioning at least one potential COI, and 113 reporting conflicts of interest by the clinical experts. The conflicts of interests were reported in relation to 37 pharmaceutical companies (Abbott, AbbVie, Achillion, Alnylam, Astellas, Bayer, Biocompatibles, Boehringer Ingelheim, Bristol-Myers Squibb, BTG, Chugai, Conatus, Falk Pharma UK, Gilead, GSK, Idenix, Intercept, Janssen, Merck, Merck Soreno, MSD, NHS England Ebola Response Team, Norgine UK, Novartis, Pfizer, Pharmasett, Presidio, Regulus, Roche, Sanofi, Schering-Plough, Springbank, Tekmira, Tibotec, Vertex, ViiV, Virco, Wilson Therapeutics) one medical device company (OrganOx,) and one medical service company working with drug companies (Alcura). We counted subsidiaries (Biocompatibles, Chugai, Merck Soren, Vertex and ViiV) as separate entities. We excluded form the analysis one COI ("worked with"), reported in relation to a non-commercial entity (NHS England Ebola Response Team). In addition to investigating the scholarly outputs, we inspected AbbVie's, Bristol-Myers-Squibb's, Gilead's, and Janssen's websites looking for any forms of individual research support offered to UK-based clinicians. We established that only Gilead reported the provision of five research fellowships ("Gilead Fellowships") between 2009 and 2013 to four of the clinical experts. The potential COI categories reported in Table 1 were derived inductively based on information from the potential COI declarations and the Gilead website. The analysis involved aggregating lower-level categories based on their semantic similarity, with all reported potential COIs being included in the analysis. The *"grant & research funding"* category includes the following potential COIs: "grant funding", "grants", "grant support", "received funding", "grant", "research funding", "research grant support", "research support", "research grants", "supported in clinical research", "department received research grants", "received educational grants" and Gilead Fellowships. The *"payments"* category covers "received financial support", "received payment", "received fees for participation in review activities", "received honoraria", "honorarium", "honoraria", "personal fees", "fees", "received educational travel grants", "received travel expenses", "travel sponsorship". The *"dissemination"* category comprises "speaker", "speaker fees", "served as a speaker", "speaking", "paid speaking engagements", "received

speakers honoraria", "service on speakers bureaus", "member of speakers bureaus", "on speakers' bureau", "acts as a speaker", "teaching", "received funding for lectures", "received payment for lectures", "gave […] paid lectures", "received honoraries [sic] (lectures)", "lecture fees", "participated in presentations). The *"consultancy and review"* category consists of "provided consultancy", "consultancy fees", "consulting fees", "served as a consultant", "financial compensation for consultancy activities", "consulting", "consultancy", "consults", "consultant", "consultancy payments", "consulting role", "consulted", "review panels". The *"advisory boards"* category covers "advisory board fees", "served on advisory board", "advisor", "holds board membership", "acted as advisor", "advisory boards", "member of advisory boards", "advises", "acted in an advisory capacity", "acts as advisor", "advisory fees", "advisory roles", "received honoraries [sic] (advisory boards)", "advisory role", "avisory [sic] committees", "board membership", "sat on advisory boards", "advisory board member", "attended advisory boards"). The *"work"* category includes "contract with institution", "medical director and co-founder", "medical director", "shareholder", "served as investigator", "acted as clinical investigator or chief investigator", "acted as principle [sic] investigator", "participated in clinical trials".

Table 3 Potential conflicts of interests (COIs) of different categories of clinical experts involved in the appraisal and reimbursement of sofosbuvir-based therapies

	AbbVie		Bristol-Myers-Squibb		Gilead		Janssen		Total		
Expert category	Experts with a COI	Number of COIs	Experts with a COI	Number of COIs	Experts with a COI	Number of COIs	Experts with a COI	Number of COIs	Experts with a COI with	Number of COIs	Number of experts
Contributed to designing Early Access Programme	2	10	3	12	3	11	3	13	3	158	3
Member of Hepatobiliary and Pancreas or Infectious diseases CRG	5	14	5	19	11	26	8	23	16	221	33
Contributed to sofosbuvir or ledipasvir-sofosbuvir appraisals	2	11	3	15	5	17	6	20	7	141	8

Note: For the COI categories used to carry out calculations and the list of commercial entities see note to Table 2. The numbers of COIs are not summarised across the columns as three experts fall under more than one expert category (see note to Table 2).

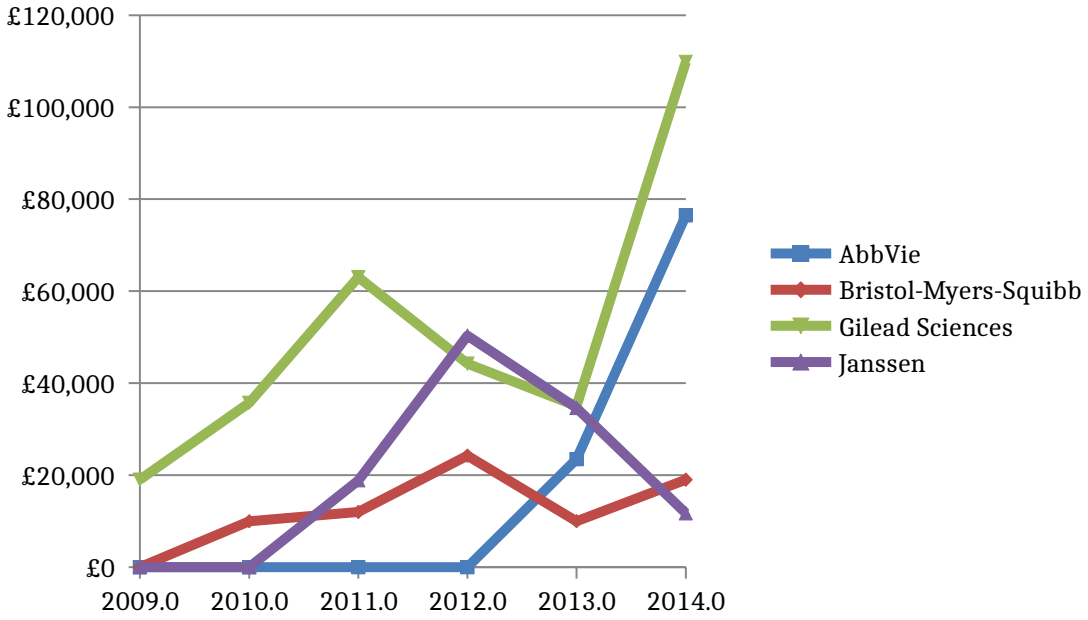
Table 4 Sources of research funding of different categories of clinical experts involved in the appraisal and reimbursement of sofosbuvir-based therapies

Expert category	AbbVie	Bristol-Myers-Squibb	Janssen	Gilead	Other industry funding	**Industry funding total**	nsCharities and non-governmental	Foundations	Universities	Medical specialty organisations	**Third sector funding total**	ch UK National Institute for Health	US National Institutes of Health	Publicly funded Research councils	Public healthcare organisations	Other public funding	**Public funding total**	**Funding total**
Contributed to designing EAP	2 (2)	3 (1)	3 (7)	3 (11)	3 (9)	3 (28)	1 (4)	3 (4)	2 (4)	1 (1)	3 (9)	1 (3)	1 (1)	2 (3)	3 (3)	3 (6)	3 (12)	3 (38)
Member of Hepatobiliary and Pancreas or Infectious diseases CRG	1 (1)	2 (2)	4 (7)	11 (19)	11 (22)	17 (47)	14 (17)	12 (13)	13 (19)	0 (0)	18 (34)	13 (18)	11 (8)	13 (12)	9 (9)	15 (16)	19 (43)	25 (91)
Contributed to the sofosbuvir or ledipasvir-sofosbuvir appraisals	1 (1)	0	1 (1)	3 (8)	4 (4)	5 (14)	4 (4)	4 (3)	3 (3)	1 (1)	4 (6)	3 (2)	5 (3)	3 (3)	3(4)	7 (5)	7 (12)	7 (27)
Total	3 (3)	4 (2)	7 (10)	15 (22)	16 (26)	23 (59)	17 (19)	17 (14)	16 (20)	2 (2)	23 (38)	15 (19)	14 (9)	16 (14)	12 (11)	22 (22)	26 (53)	32 (114)

Note 1. The table reports the number of clinical experts (without brackets) and projects (in brackets) supported by different types of funders.

Note 2. The names of project funders were provided in 98 outputs listing the clinical experts involved in the appraisal and reimbursement of sofosbuvir-based therapies as authors, and following additional searches using clinical trial names or numbers, we identified further six funders. Within these outputs 70 mentioned project names or numbers, as identified by, for example, clinical trial, grant names or numbers, research ethics approval numbers and other identifiers. Funder names were provided in 21 outputs listing the clinical experts as collaborators, with 13 outputs mentioning project names. We screened all outputs, merging those referring to the same projects and duplicating those reporting findings from more than one project. Following this procedure we arrived at the list of 114 unique projects. A possible limitation of this approach is that not all outputs mentioned specific project names or numbers. In these instances, the uniqueness of a project was evaluated based on through reading of the outputs. We also looked for individual research support to clinicians on AbbVie's, Bristol-Myers-Squibb's, Gilead's, and Janssen's websites (See note to Table 2). Following this approach, we considered five "Gilead Fellowships" awarded to four of the clinical experts between 2009 and 2013 as projects sponsored by Gilead and included them in the analysis.

Figure 1 Trends in financial donations made to patient organisation and charity consultees in the NICE appraisals of sofosbuvir or sofosbuvir-ledipasvir by Gilead and its major competitors (financial years 2009-2014)



Note: We compiled the list of 30 patient organisation and charity consultees by merging the consultee matrices used by NICE in the sofosbuvir and ledipasvir-sofosbuvir appraisals. From June to August 2015 we conducted searches on the Charity Commission website, establishing that 20 of these organisations submitted, on the whole, 94 yearly financial statements, starting with the financial year ending 2008/09 and through to the financial year 2013/14. For each consultee, we established the list of donors and the amount of financial transfers in each financial year. The figures we report for Gilead include both donations and Gilead Fellowships.

Table 5 Breakdown of financial donations made to patient organisation and charity consultees in the NICE appraisals of sofosbuvir or sofosbuvir-ledipasvir by Gilead and its major competitors (financial years 2009-2014)

	Pharmaceutical companies			
NICE appraisal consultees	AbbVie	Bristol-Myers-Squibb	Gilead Sciences	Janssen
African Health Policy Network	£6,000	£2,000	£43,500	£5,300
Black Health Agency	-	-	£5,000	-
The Hepatitis C Trust	£50,500	-	£80,750	£44,805
National AIDS Trust	£31,000	£48,250	£84,084	£14,000
Positively UK	£12,500	£15,000	£50,500	£51,435
Terrence Higgins Trust	-	£10,000	£43,000	-
Total	£100,000	£75,250	£306,834	£115,540

Note: See note to Figure 1.

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