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David Hughes, Shane Doheny

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Doing evidence-based medicine? How NHS managers ration high-cost drugs

David Hughes, Swansea University

Shane Doheny, Cardiff University

Corresponding author:

Professor David Hughes
Department of Public Health, Policy and Social Sciences,
Swansea University,
Singleton Park,
Swansea SA2 8PP,
Wales, UK.
d.hughes@swansea.ac.uk
Tel: 01792 602114

Introduction

Evidence-based medicine (EBM) remains a powerful, albeit controversial, influence in Western healthcare systems, but social scientists have found it difficult to observe just how EBM is enacted in the work of managers and professionals. This paper helps to fill this gap by examining the deliberations of a Welsh National Health Service (NHS) Individual Patient Commissioning panel (IPC) panel charged with deciding whether to fund high-cost drugs for candidate patients put forward by medical consultants. Even though there is a persistent effort in the panel to link decisions to evidence, this occurs within a hybrid decision environment in which organisational and lifeworld considerations also enter deliberations. We describe how panel members use three discursive repertoires to make sense of cases as they set out to "do" evidence-based decision making. We argue that repertoires are combined flexibly to take account simultaneously of evidence of drug efficacy, procedural rules that limit patient eligibility, and political, legal and normative realities. We examine shifts between what we term empiricist, procedural and contingent repertoires, deployed to produce decisions that combine a form of evidence-based scientific practice with pragmatic judgments about the best use of scarce resources. Although panel members manage most cases without any great sense of cognitive dissonance, there are occasions when these repertoires come into tension and induce worries about the rationality of what can become a rationing process.

Although the data we present were collected some years ago (see Methods section), funding request panels remain a highly topical policy issue. NHS Wales published an independent review report in January 2017 and issued new guidance on what are now known as individual patient funding requests (IPFR) in June (NHS Wales 2017a; NHS Wales, 2017b). England launched a consultation exercise on Individual Funding Requests (IFR) policy in October 2016 and published new guidance in November 2017 (NHS England 2017a; NHS England, 2017b). In both countries concerns were expressed about the limits of evidence-based decision making in areas such as the handling of "exceptional" cases and rare diseases (Heale and Syrett, 2018; Hughes and Doheny, forthcoming).

Moreover, although the nature of drug requests may be changing and the balance between drug and non-drug requests shifting, the overall flow of cases considered by panels continues to be high in both countries (Iacobucci, 2017; Routledge, 2017).

Syrett (2007) argues that over time responsibility for allocating healthcare resources has moved away from individual clinicians to groups of professionals and managers. He writes of the emergence of "normative and technical criteria" and the creation of procedures and institutions to manage allocative decisions. The latter include the National Institute for Health and Care Excellence (NICE), IFR panels and other underpinning technology for EBM. Calnan, Hashem and Brown (2017) argue that, within this institutional framework, actors pragmatically combine tactics to navigate through the layers of complexity and uncertainty to make what are formally evidence-based decisions. According to Calnan (2018), front-stage decision making by institutions such as NICE depends for its operationalisation on backstage allocative decisions in forums such as IFR panels, which interpret guidance using practical rationalities.

To date, social scientists studying EBM have focused largely on its core ideas and ways of seeing, and its controversies and ongoing development, rather than examining its interactional enactment in particular settings. Researchers have *inter alia* examined EBM as a social movement (Pope, 2003; Traynor, 2009), a field of discourse (Reid, 2014; 2016), a set of collectively-constructed mindlines (Gabbay and Le May, 2004; 2010), and a form of rhetorical action (Greenhalgh and Russell, 2006). They have criticised the biases that arise from the structural position of clinical research and EBM's cultural assumptions (De Vries and Lemmens, 2006). They have drawn attention to implementation gaps (Dopson et al., 2003), the redefinition of autonomy and relationships involved (Timmermans and Berg, 2003), and professional resistance (Bhandari et al., 2003; Pope, 2003; Will, 2005; Armstrong, 2007; Traynor, 2009), and argued that EBM cannot remove judgement from clinical decision making (Mykhalovskiy, 2003; Mykhalovskiy and Weir, 2004; Upshur, 2005; Kelly and Moore, 2012). However, data for these studies come mainly from textual materials and interview accounts

rather than observation of professionals and managers at work. The one example of interactional discourse analysis in this area we were able to locate, a study of nutritionists' understandings of EBM (Bouwman and te Molder, 2009), relied on analysis of research interview discourse.

An interesting strand of anthropological work discusses the potential value of ethnographic studies of EBM (Lambert, 2006), but has so far concentrated mainly on describing the variegated forms and ever-changing nature of the "amorphous creature" that is EBM (Lambert 2009: 17). A recent special issue of *Medical Anthropology* explores the practice of EBM in a range of national contexts and settings and concludes that it is not "an ideal-type, everywhere the same", but rather a diverse collection of "translations, negotiations, adaptations, and successes and failures in its deployment on the ground" (Brives, Marcis and Sanabria, 2016: 369). The special issue offers a synoptic perspective on EBM as a global movement, and contains case studies of an Austrian bariatric surgery pre- and aftercare service, a French tuberculosis control project, and how Portuguese child psychiatrists and developmental clinicians diagnose ADHD. Useful as these reports are, they again do not present detailed interactional data on the *in situ* enactment of EBM.

The past research that most resembles the present study is Russell and colleagues' investigation of the work of three IFR panels in London and the South East of England (Russell and Greenhalgh, 2012; 2014; Russell, Swinglehurst and Greenhalgh, 2014). These are similar to the Welsh IPC panel considered here, and both studies used ethnographic methods with a focus on language and social interaction. Data for the English study included email exchanges, field notes of panel discussions and analysis of one audio-recorded panel meeting covering seven cases. The study considers the framing of rationing decisions in "rational" versus "human" terms, the discursive practices used to introduce "affordability" into deliberations, and how the notion of "low value" procedures is dialogically constructed (using the case of cosmetic breast surgery). However, although the English study touches on key issues of effectiveness and exceptionality (see below), it does not set out to analyse case discussions as situated enactments of EBM or examine how they are framed to

combine attention to the individual case with trials evidence. An earlier paper by the present authors (Hughes and Doheny, 2011) examines how panel deliberations are adapted over time to accommodate changing NICE guidance, and again did not consider how the participants "do" EBM.

The image of EBM as an 'amorphous creature' suggests that no single form of decision making will be found, even in bedside clinical practice. Rather EBM is enacted in various hybridized forms of discourse that strive to connect outcomes with evidence, and in the case of the IPC to combine empiricism with procedural and contingent concerns.

EBM as an ensemble of discursive repertoires

The present paper benefits from Gilbert and Mulkay's (1984) seminal work on the discursive repertoires used by scientists, and their identification of a formal empiricist repertoire that exists alongside an informal and contingent repertoire (1984: 40). The empiricist repertoire is commonly used in research papers and is characterised by a conventionalised and highly impersonal characterisation of laboratory work, as well as minimal reference to the authors' own beliefs, decisions and judgements. In essence the "[e]mpiricist discourse is organised in a manner which denies that its author's actions are relevant to its context" (1984: 56). Gilbert and Mulkay contrast this repertoire with an informal "contingent" repertoire, via which "scientists presented their actions and beliefs as heavily dependent on speculative insights, prior intellectual commitments, personal characteristics, indescribable skills, social ties and group membership" (1984: 56).

Gilbert and Mulkay (1984) do not claim that these two repertoires are the only ones deployed in scientific work; they cite Halliday's argument that discursive forms are shaped by the contexts in which they are produced. Their research is based on textual materials rather than spoken interaction, and they allow that other repertoires may emerge in other contexts. Our paper is concerned with the work of a panel that acts as the gatekeeper for access to expensive drugs, under conditions where the purchasing NHS commissioner has insufficient resources to fund all requests. In this context the

discourse of meetings needs both to point to the science that shows that a drug is efficacious and to provide a rationale for deciding that a particular patient should receive a drug that is not routinely purchased. This leads panel members to deploy a third procedural repertoire centring on the "exceptionality" of the case; the special characteristics that justify use of the drug on an exceptional basis. The absence of exceptionality does not in itself establish a scientific basis for withholding a drug, since many drugs that at one stage were not routinely funded may later be provided for a wide range of patients following a favourable NICE technology appraisal. Rather exceptionality can be seen as a pragmatic strategy for limiting provision of a high-cost drug to a small subset of patients, based on an existing state of knowledge that says that its value for the generality of patients remains unproven and the cost is therefore too high. The assessment of exceptionality may thus be seen as the point in many panel deliberations where the science of what works collides with the practical reality of rationing healthcare.

It is worth adding that the empiricist repertoire resembles, but is not the same as, the discourse of the medical case presentation (Anspach 1988; Hobbs, 2003). Just as the empiricist repertoire of the scientist removes his/her agency from a scientific report, the medical case presentation "omit[s] the physician, nurses and other medical *agents* who perform procedures or make observations" (Anspach 1988: 366) by using the passive voice. But although the medical case presentation de-personalises the patient by drawing on an "impersonal" vocabulary to describe cases in terms of diseases, procedures or organs, it recognises the individuality of cases by incorporating the details of different patient histories, illness trajectories and responses to particular treatments. By contrast, the empiricist repertoire visible in IPC panel discussions de-emphasises individuality and instead prioritizes evidence that relates to patient populations, cohorts or subgroups.

Methods

Data presented here were collected as part of a larger project on commissioning and contracting in the NHS, which involved observations and interviews in four case study localities in England and

Wales (Hughes et al, 2011a; 2011b). Given that this study was concerned mainly with cross-national differences in secondary care contracting and the evolution of policy, our project outputs centred on these areas and we did not make full use of our corpus of audio-recorded IPC data. Early use of the IPC data was anyway inhibited by ongoing judicial review proceedings affecting a case we had observed, and making this part of our research particularly sensitive (Hughes, 2018). It is only some ten years later that the authors have had time to return to it. That time gap is an acknowledged weakness, but as we argued in our introduction, allocative panels remain a controversial and highly topical issue. In England the 2017 guidance has resulted in minor procedural changes, but effectiveness and exceptionality remain as the central principles guiding panel decisions. The new Welsh guidance has led to more substantial changes that diverge from English policy (see Conclusion section), but again panel decision making continues to be conceived as primarily an evidence-based process. The numbers of cases going to panels in both countries remains high. Consequently we believe there is value in further analysis of a rare data set on a hard-to-research arena for ”backstage” decision making.

Our IPC data were gathered between the months of April and October 2008. During this period, one or other of two researchers attended and recorded IPC panel meetings convened and hosted by a Welsh Local Health Board (LHB), and responsible for making decisions regarding the provision of high-cost drugs. Under the regional IPC policy, only treatments whose cost exceeded £2,000 per course or £20,000 per annum could be considered by the panel. All but four of the observed funding requests involved cancer drugs, and this appeared to be the general pattern at that time, apart from a brief period when multiple requests were made for the macular degeneration drug Lucentis (for a list of drugs requested see: Hughes and Doheny, 2011, supplementary material). NHS research ethics committee approval and access approval from the LHB were obtained, and all panel members signed consent forms (see: Hughes, 2018 regarding ethical issues raised). Eleven IPC panel meetings were attended, involving 23 referred cases (some discussed in two or three meetings). These formed an unbroken sequence with the exception of one missed extraordinary meeting (not on the

regular meeting day) about which the panel had failed to inform the researchers. Observation of IPC meetings was supplemented by attendance at three policy review panels (which consider appeals), interviews with key participants and reading of relevant background documents. We make greater use of the interview data in two companion papers (Hughes and Doheny, 2011, supplementary material file; Hughes and Doheny, forthcoming), and the interviews are only used as background here. A fuller explanation of the study methodology can be found in Hughes (2019).

The IPC meetings were transcribed in full and the transcripts subjected to analysis, paying attention to sequential organisation, emergent patterns and themes. We employ a form of sociological discourse analysis influenced by interactionist sociology and ethnomethology. We see this as a type of linguistically-sensitive ethnography, building on earlier studies that have sought to ground interactional studies more firmly in detailed sequences of spoken interaction (Cicourel, 1968, Strong, 1979; Silverman, 1987). Our observations and reading of the transcripts brought to our attention a number of ways in which panel members framed cases and linked decisions to IPC policy or other considerations. These initial ideas provided the basis for identifying themes and associated codes that we used to classify and label passages from the transcripts. Our analysis mixed deductive analysis based on the application of concepts from relevant literature, such as Gilbert and Mulkay's (1984) work, with inductive analysis involving ideas emerging from our data. The extracts chosen for inclusion in the paper were selected because they provided clear and representative illustrations of relevant processes.

All but one of the panel members were LHB employees. The panel was chaired by the LHB medical director, and attended by the assistant director of commissioning and information (ADCI), nursing director (ND), finance director (FD), director of clinical development (DCD), IPC officer (IPCO), and a pharmacist advisor (PA), who was released part-time to support the IPC panel from his main appointment in what at that time was an NHS Trust hospital. Of these the PA, FD and IPCO are male and the rest female. Clinical expertise came from the chair, whose background was in general

practice and pharmacology, and other managers with backgrounds in nursing and midwifery. Patients and referring hospital consultants did not attend. The meetings were held on every second Tuesday morning (with some breaks in the summer due to absences for holidays) in the LHB's building on a local enterprise park, around a large table in the office of the Director of Clinical Development.

The procedural basis of decisions

As a response to concerns about a "postcode lottery" of unequal geographical provision, many NHS purchasers have chosen to adopt shared policies on handling referrals for high-cost drugs. The commissioning panel that we observed relied on a regionally agreed ethical framework, which in turn was based on the framework developed by the Thames Valley Priority Setting Unit, a framework influenced by bioethicists such as Daniels (2000). This aims to achieve "distributive and procedural justice", and sets out the following principles of decision making.

(1) Consistency of process – the principle that concepts and principles used in one case should be applied in subsequent cases of sufficient similarity
(2) Economic considerations – the duty of the commissioner to not exceed budget and to be mindful of the implications of diverting resources
(3) Principle of rescue – the principle that all referrals should be considered
(4) Principle of exceptionality – the principle that any case should meet with the condition of exceptionality to receive funding
(5) Evidence of effectiveness – the principle that interventions must meet with the condition of clinical effectiveness to receive funding
(6) Transparency
(7) Non-discrimination
(8) Autonomy, individual choice, benefice and non maleficence
(9) Independence

Distributive justice is concerned with the need to distribute scarce resources in a fair and just manner, and relates to economic considerations, rescue, exceptionality, effectiveness and non-discrimination.

Procedural justice relates to process, as reflected in the principles of consistency, non-discrimination, transparency and independence.

EBM applies epidemiological techniques to individual patient care in an attempt to prevent the overuse of ineffective treatments, the underuse of effective treatments, and the misuse of treatments whose effectiveness has not been established (Brown, Crawford and Hicks, 2003: 83). Two of its main tools are the randomised controlled trial (RCT) and the meta-analysis of small-scale studies (Moreira, 2007: 182). The ethical framework identified above represents an EBM tool insofar as it takes up certain EBM assumptions, and offers a technique for reaching decisions. Like EBM, the ethical framework addresses the problem of providing drugs to treat conditions in the absence of definitive knowledge about the effectiveness of the intervention for a given patient.

In theory the panel should take account of all seven principles above, but we argue that the panel's operationalisation of the ethical framework prioritises the two principles of effectiveness and exceptionality, in that order. EBM represents an epistemological framework that recognises a hierarchy of effectiveness evidence that favours RCTs and meta-analysis, and this is reflected in the ethical framework's statement that:

> The LHB should not support the use of interventions for which evidence of clinical effectiveness is either absent or too weak for reasonable conclusions to be reached. The LHB will endeavour to seek and obtain the best available evidence of clinical and cost effectiveness to an acceptable standard. (Regional Ethical Framework, 2007)

From 2003 NHS Wales guidance (Welsh Health Circular WHC[2003]109) required LHBs to fund implementation of NICE technology appraisal recommendations, and so clinical effectiveness was assessed in relation to available guidance from NICE and the All-Wales Medicines Strategy Group (AWMSG).

This framework allows the commissioner to fund treatments only when they are clinically effective, but also requires that funded patients must be shown to be exceptional, in that their characteristics differ significantly from those of the generality of patients with a given illness condition.

> In order for funding to be agreed there must be some unusual or unique clinical factor about the patient that suggests that they are significantly different to the general population of patients with the condition in question by being likely to gain significantly more benefit from the intervention than might be expected from the average patient with the condition. (Regional Ethical Framework, 2007)

This places a responsibility on the panel to evaluate the submissions made by medical consultants, but also to consider the case in relation to the wider population of patients with the given illness condition. In effect, the panel are duty bound to consider the evidence at hand in order to give a medically and scientifically-based reason for their decision (see Newdick, 2006: 206-207).

This framework provides the panel with a methodology for explicit rationing linked to EBM Moreover it drives the EBM agenda forward by ensuring that local panels do not merely react to NICE or other guidance, but actively monitor the emerging scientific evidence in ongoing deliberations regarding particular cases. In the sections that follow we examine how the empiricist repertoire that this involves combines with the procedural and contingent repertoires already mentioned.

The empiricist repertoire

In the meetings observed the PA introduced the case by summarising the content of the referral letter, and giving his assessment of relevant scientific evidence regarding drug efficacy. Typically the Medical Director would comment on the case presentation and then open the floor for other panel members to express their views. The meetings move quickly to consider clinical effectiveness

evidence that generally relates to RCT findings regarding results for patient populations and sub-groups rather than individuals. The PA would come to meetings with prepared notes on each case that could touch on such matters as current NICE guidance, other advice from bodies such as AWMSG and the National Public Health Service, and findings he had assembled from published reports concerning the requested drug as applied to the relevant disease condition. He would offer an interpretation of the strength of evidence of effectiveness in respect of particular disease stages or patient sub-groups, and an assessment of likely benefit for the referred patient in relation to those categories.

Generally the opening presentation by the pharmacist closely resembles the formal empiricist repertoire discussed above. The panel enacts a form of EBM by moving quickly to review the types of evidence that it values, so that they can present their decisions as outcomes based on science rather than judgements of value. In Extract 1 the referral is introduced not in terms of individual patient characteristics, but rather evidence about the effectiveness of the drug for a given class of patients. Gleevek (imatinib), the standard therapy for gastro-intestinal stoma tumours (GIST), has not been effective in this case, and this opens the possibility of prescribing Pfizer's Sutent (generic name sunitinib), which is licensed as a second-line treatment for GIST, but not yet approved by NICE. The PA moves quickly to construct a case presentation based on expert scientific knowledge – the indications for which Sutent is licensed, (line 6) and what he has found out from a recent study concerning patients who may benefit from second-line alternatives to Gleevek (lines 8-10). He mentions (at line 13) that he has talked with the referring consultant's registrar, but only to confirm that the first–line treatment has failed. It is only after presenting the research evidence that the PA makes reference to the referral letter (lines 44-48). Even then he avoids reference to biographical information, repeats that Gleevek has not worked, notes that the consultant has omitted to make a case for exceptionality, and mentions that the treatment plan would have only the general aim of stopping the tumour growing. Conventional medical discourse as described by Anspach (1988) and containing information on the case history, individual circumstances and care plans is almost entirely absent from the panel discussion.

The PA's summary of the research evidence is not easy to follow without reading the original reports. The *Lancet* trial (Demetri et al., 2006) discussed took a large group of patients who were resistant to, or intolerant of Gleevek, and found that median time to tumour progression (MTTP) was 27.3 weeks for those receiving sunitinib and 6.4 weeks for those given a placebo. The MD interrupts the PA's presentation to mention the related finding that the median duration of progression-free survival also quadrupled for the sunitinib group at 24.1 weeks compared with 6.0 weeks for the controls (line 22). The PA responds by giving the headline MTTP figures (line 23) and saying that the MD's figures relate to progression-free survival, but it is unclear whether other panel members understand this distinction. This study was "unblinded" when the improved outcomes of the sunitinib group became apparent, so that all patients then received the drug, and this is what the PA tries to explain as he elaborates on the "ropey" nature of this part of the study (lines 26-30). The researchers were unable to calculate an overall survival rate because more than half the patients were still alive at the close of the study, but this is not clearly communicated in the discussion.

Extract 1

1 PA: Last one. [uses initials as patient identifier]
2 IPCO: Came in this morning
3 PA: Right okay. Here we go. I will try and do this again. This is a little bit more tricky. This is
4 Sutent for GISTs which is gastro-intestinal stromal tumours.
5 FD: Do they say sunitinib for that?
6 PA: That's it. Yes, it is licensed for this. It's licensed, as it says on the top of my sheet of
7 paper, for treatment of metastatic GISTs after failure of Gleevek treatment due to resistance or
8 intolerance. What I have managed to find out is that in advanced cases of GISTs 5% show
9 primary resistance, 14% develop early resistance through secondary or acquired resistance
10 developing after a mean of two years. Okay? That's what I have found out so far. What has
11 happened with this lady is… now to be honest with you we have got a lot of people on
12 Gleevek for GISTS, which is NICE approved, okay. This is the first failure that we have had
13 from what I can understand. Having spoken to Dr Phillips' Reg*. I think it was Dr Phillips'
14 Reg just because I was interested in this and why we suddenly had this come through. Now it
15 is a really tricky study to interpret because of...going back to the evidence...the interim
16 analysis again proved that overall survival was improved so you have got a hazard ratio of
17 0.49 which means there is a 51% improvement in benefit… of not dying. If I've got that the
18 right way round. Median overall survival they couldn't work out because the interim analysis
19 when it was stopped there were still more than 50% of the sunitinib people still alive. Okay,
20 which makes this potentially it's...that is good but it just means I can't give you a number of
21 months behind it. Right? But it is a good thing. If you look at median time to progression,

alright, that in oncology is meant to be a very good marker
MD: Twenty-four to six.
PA: …Yeah, It is huge. It is a big big difference is that… twenty-seven versus six weeks. So from the point of view of the evidence I am... Again the median progression-free survival is twenty-four weeks versus six. The figures are all relatively similar, okay? They've updated the analysis from the first study and that's where it gets really ropey. They have put an overall survival in there. The problem with it is this crossover from the placebo group onto sunitinib, and it still shows progression free survival. Although it has gone from twenty-seven to twenty-four in the people who were on sunitinib. So it is working.
MD: It works, Okay?
PA: From an evidence point of view it is working
MD: Published?
PA: Lancet published one
MD: Lancet, good
PA: And the other one I'm sorry I was trying to finish this. It is here...Lancet and the other one is European Journal of Cancer, but it's a review of all the evidence. So it's not… secondary referencing that would be… That's not so great, but they do quote overall survival. But not having read the original paper it is very difficult to...
FD: Is it NICE approved?
PA: No it is not NICE approved again
MD: Lancet is pretty good
PA: Oh yeah.
MD: Yeah. So it is published evidence of efficacy
PA: This lady has basically been on Gleevak. No response. Progressive. So they doubled the dose and still had disease progression. So this is the drug not working. Okay. Dr Phillips hasn't put any exceptionality down at all, other than "Implication of funding for progressive disease". What he plans to do is give the drug. And how they monitor it is CT after 3 months and see whether you have actually stopped the tumour from growing. That is what I have got.

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*Pseudonyms are used throughout. "Reg" is an abbreviation of registrar, the highest grade of junior hospital doctor working under a consultant.

The persuasive power of the PA's presentation comes from using research evidence from reputable sources to suggest likely benefit. This sequence differs from a conventional medical case presentation in that the PA provides an informal review of study findings regarding a particular patient population (those resistant to, or intolerant of Gleevek), rather than providing a detailed report on the individual patient referred. Little is said about the distinctive clinical trajectory of the patient; all that is established is that RCT data suggest that the referred case falls within a group for whom the drug is likely to work. While the presentation takes the general form of a scientific review, it lacks the comprehensiveness or detail of a published paper, and is accepted as a pragmatic verbal

report prepared in the short time available. The relative lack of sophistication of the brief verbal account becomes evident if it is compared with the explanation of the limitations of this trial in NICE's (later) 2009 technology appraisal (TA179). In 2008 there is no NICE approval (line 40), but journal names are mentioned and the status of *The Lancet* as an authoritative source flagged (lines 42-43). This enables the MD to point to "published evidence of efficacy" as an important decision criterion (line 44). There is a striking absence of reference to lifeworld factors such as personal circumstances, deservingness or social status, so that talk remains within a seemingly objective empiricist frame. The general pattern of panel discussions is that efficacy must be established before moving to a second criterion of exceptionality that is flagged towards the end (line 47).

The procedural repertoire

This is where a shift in footing (see: Goffman, 1981) occurs; attention now turns from whether the drug is efficacious to whether the patient is in a category that will justify departing from the LHB's stance of not purchasing the drug for the generality of patients (line 51 below). Directly following Extract 1 talk moves to address this procedural repertoire. An easy path to establishing exceptionality exists in this case because the patient falls into a 5% subgroup for whom Gleevek is ineffective; she has shown no response to an increased dosage and so lies within the target group for Sutent (sunitinib) (lines 50-55).

Extract 2

51 MD: We would need to find exceptionality first wouldn't we?
52 PA: Well if you say 5% show primary resistance this lady showed no response with the first
53 dose and still showed disease progression with the higher dose. So you are talking...the
54 information in The Lancet journal says in advanced just 5% show primary resistance and this
55 to all intents and purposes...I can't say hand on heart say that...I think is primary resistance.
56 Because we have had no response with the first dose. He increased the dose and she still had
57 disease progression in fact no response at all.
58 MD: To this drug
59 DCD: To Gleevek
60 PA: To Gleevek. The request is for sunitinib then.
61 MD: That's what...you are talking about exceptionality now.
62 PA: You asked does this fall into a minority group and I think they fall into this 5% bit I put
63 on here.

FD: What was the previous drug she was on
PA: Gleevek which is...
FD: How much does that cost?
PA: Similar to this - it is going to be cost neutral.
FD: So we funded her on that...
PA: But that is NICE approved. This has got no NICE, no All Wales Medicines Strategy Group. No nothing. Yet
FD: But the evidence
PA: The evidence is a lot stronger than...when Gleevek first came out one of the things that I always found amazing is that it is the first time I ever heard anyone saying 100% response rate to GIST so that's the first time I had ever had something as remarkable as that
FD: But the drug she is on at the moment she is not responding to...
MD: Yeah
PA: She is on a high dose of that so she is up to about 25 maybe 30 thousand pounds
FD: That is efficacious. That is NICE approved in terms of being effective. This has got similar results
PA: Not as good no. But these are the resistant patients.
FD: Not as good but a similar price and everything so presumably similar arguments apply
MD: We have done that before we have just made a switch...except we set a precedent if we fund it. Even though we say "well you know the costs are the same". We still have to agree
DCD: But we are funding for exceptional. We are only funding for those with primary resistance. We would only be funding because she is not responding
MD: Because she is exceptional
DN: She is exceptional isn't she?
MD: I would say she is exceptional and we should fund.
PA: Fantastic. I will work on the letters the next few days Tom.
IPCO: Fine

IPC Panel May 20th

Although the exceptionality criterion might deny a drug to patients who would benefit, this is largely invisible here because of the patient's resistance to Gleevek and the fact that Sutent is licensed as a second-order treatment for those in her situation. The remaining hurdle is the absence of NICE approval (lines 69-70), but the panel appears to conclude this is outweighed by the effectiveness evidence. The PA works to retain the scientific framing of the decision by repeating that the patient falls within the small subgroup identified by research as the one likely to benefit from Sutent, and is thus exceptional (line 62- 63). A lifeworld consideration intrudes into talk in the form of the cost implications of providing the new drug, but as the cost is similar to Gleevek this is not a major concern. The panel moves smoothly from the empiricist repertoire concerned with proof of efficacy on to the procedural repertoire concerned with exceptionality, while still retaining a sense of scientific objectivity; the decision taken aligns with research findings on GIST subgroups and accepted

treatment options. The MD is able to say that they have not established a precedent that will cause future problems, because only a small subgroup of GIST cases (a minority of patients) are involved (lines 82-85).

It is important to note that 14 of 23 funding requests observed by us were denied, usually though not exclusively on efficacy grounds. Determinations that a drug will not benefit a patient might be controversial but did not cast doubt on the legitimacy of the decision making process because disagreements were about the interpretation of research evidence rather than the central relevance of effectiveness and exceptionality. However, in a handful of observed cases Sutent appeared to offer probable benefit, but exceptionality was deemed to be absent. This came to a head in one meeting when the panel questioned the fairness of its decision-making framework.

Apart from its application to GIST cases, Sutent is licensed for the treatment of renal cell carcinoma, and the case that follows involved a male patient said to be in an "intermediate prognostic group", whose life might be extended significantly if given the drug. In this case discussion the PA reported the results a recent trial published in the *New England Journal of Medicine* (*NEJM*) (Motzer, et al, 2007), which showed that patients treated with the drug survived around 14 months longer than the control group. Although AWMSG had previously advised against use of Sutent for kidney cancer on cost grounds, the panel found this new study persuasive and concluded that there was good evidence of effectiveness. But while the empiricist repertoire provided strong objective grounds for approving funding, it transpired that the working definition of exceptionality employed by the panel meant it could not approve the request.

Extract 3

1 DCD: From an efficacy point of view we think it stacks up.
2 PA: Based on what has been presented so far we have no reason to doubt the information
3 that's here.
4 DCD: Okay. So the exceptionality that he has put in here is correct. There's nothing else that
5 this person could have is there?

6 DN: How many patients would be intermediate prognostic group?
7 PA: Fifty per cent.
8 DN: So therefore based on benefiting more than the rest of the population they wouldn't
9 because the rest of the population would benefit from the same stuff.
10 PA: I think it was...low and intermediate were around fifty-fifty in the study. Give or take one
11 or two percent.
12 DN: So do we ask for any other areas of exceptionality for him? Or do we say that this doesn't
13 make him exceptional?
14 DCD: Based on the criteria this does not make him exceptional and I think James [PA] and I
15 are just starting to struggle with our definition of exceptionality when the drug is quite clearly
16 starting to have evidence to show that it is going to give benefit to patients.
17 PA: Because fourteen months in a disease of this....
18 DCD: It is quite prolonged
19 [segment omitted]
18 DCD: I suppose it comes back to... you know we are going to have to take a view on how we
19 treat renal cell carcinoma. Are we going to step outside?
20 FD: Our policy at the moment says no to this doesn't it?
21 DCD: Yeah
22 IPCO: Yeah but Lucentis… we've got our policy already with Lucentis haven't we?
23 FD: I am not saying stick to the policy I am just saying that if we sit here today and apply the
24 policy we have to say no to this.
25 DCD: Yes
26 PA: Yes
27 FD: Because they haven't been NICE approved and there is no exceptionality
28 DN: So then we make the decision to say no and then go down the route that they go through
29 appeals. If it goes to appeal you have to review the batch so you might as well review the
30 batch before the evidence...the evidence is the same
31 DCD: The fact that we set a precedent with Lucentis this treatment seems to be coming into
32 that
33 FD: We need to document this carefully in the minutes, isn't it? Because… whether you call it
34 new information or whatever or updated information or whatever concerned about this
35 particular drug, then we need to review it and we could then treat it in the same way as we
36 treated Lucentis as a single item issue.
37 DCD: Yeah. Okay. So we defer it until next week
38 PA: Okay. So we need to review not just this case – all of them is it?
IPC panel August 5, MD is absent on annual leave

In this case the consultant suggests that the patient is exceptional because no treatment option other than Sutent remains, but the DCD's invitation to comment on that is not taken up. (lines 4-5). Instead the issue of whether falling within the intermediate prognostic group indicates exceptionality is raised (line 6). This classification is based on the Memorial Sloan-Kettering Cancer Center scoring system and relates to predicted duration of survival. A large number of patients fall into this category, and this may have prompted the question about what percentage of patients is involved. The PA estimates

that half of renal cell carcinoma patients fall into this category. The difficulty then raised is that the ethical framework guiding panel decisions states that exceptionality involves "some unusual or unique clinical factor" that makes the case different from the general patient population. As the intermediate prognostic risk category comprises 50% of patients, and because some of the remaining 50% might also benefit from the drug, panel members find themselves struggling to agree that exceptionality applies.

The reaction of the panel is to look for another way of framing the issue that will allow them to reach the right answer. They recall how panel "policy" was adjusted to deal with Lucentis (line 22, 31-35), when wider access to the drug had been provided following the intervention of the Welsh Government Health Minister. This shifts the discussion from the discourse of EBM to the possibility that policy might again change, perhaps as a "single item issue" (lines 33-36). The discomfort generated by the case is clear from the passage when panel members admit they are starting "to struggle with our definition of exceptionality when the drug is quite clearly starting to have evidence to show that it is going to give benefit to patients" (lines 14-16). The panel struggle with the rigidities of the definition, and conclude that they have no choice but to adjust their mode of enacting EBM if they are to be able to grant these funding requests in future.

The contingent repertoire

Gilbert and Mulkay (1984) explain that contingent repertoires become visible when researchers link their scientific advances to such things as speculative hunches, social ties, personal characteristics and group membership. In the context of IPC decisions such repertoires relate to the intrusion of political, legal, moral and normative concerns into what is presented as an objective, evidence-based decision making process.

Political and legal influences tended to impact in an episodic way. IPC panels were forced to respond to political interventions affecting particular drugs, such as the Lucentis case mentioned above. In

January 2009 (after our fieldwork had finished) the Welsh Health Minister, Edwina Hart, instructed LHBs to fund Sutent, Nexavar, Avastin and Torisel, even in the absence of NICE guidance. NICE approved Sutent for first-line treatment for renal cell cancinoma in March (TA169), but funding for second-line treatment for kidney cancer was largely halted later in the year following a further NICE technology appraisal that found it was not cost effective (TA178). However, shortly afterwards the drug was approved for second-line treatment of GIST for patients intolerant of, or resistant to Gleevek (TA179).

A second preoccupation mentioned by panel members in our qualitative interviews was the prospect of legal challenges via judicial review of decisions to deny drugs. A series of cases went to the High Court at around the time of our study in respect of patients denied funding by LHBs. Although this was not reflected in an obvious way in the audio-recorded meetings, we understand that changes were made in the way panel decisions were recorded following legal proceedings brought on behalf of a patient whose case was observed by us (Hughes, 2018).

What was visible in several recorded meetings was that panel members voiced lifeworld concerns about the morality of approving expensive drugs to buy a few more months of life. One such example concerned an elderly female patient with a difficult medical history, who had had both kidneys removed, one as a result of an earlier illness, and one as a result of renal cell carcinoma that was now threatening her life. This was another patient in the intermediate prognostic group. Just before the passage contained in Extract 4, the PA has summarised the findings of the *NEJM* trial, which found a median survival of eleven months for similar patients receiving Sutent compared to four months for controls receiving interferon. The consultant has suggested that this indicates likely patient benefit. As in Extract 3, the question of the proportion of patients falling into the intermediate prognostic risk category is raised, and the panel start to move into the procedural discourse linked to exceptionality (lines 7-12) and to discuss whether a patient in subgroup comprising around fifty per cent of cases can be deemed exceptional. At that point the PA reinforces these doubts by questioning whether the issue of efficacy has been resolved. He refers back to the likely increase in survival from four to eleven

months and asks whether this is "efficacious" (line 14). This, together with the PA's clarification that the trial may not indicate overall survival, triggers a shift in footing as the DN questions the whole basis of such referrals, which she says are "wrong" (line 20).

Extract 4

1 MD: But how much? What percentage of patients come into that [the intermediate] group?
2 PA: Don't know that
3 MD: We need to know that because then we can say whether that patient is outside the
4 normal for that...which is one of the reasons whether we consider sub-groups or not. We
5 have always had that problem haven't we?
6 PA: I can tell you how many people were in the different sub-groups in the study.
7 MD: But also we are getting into the realms of exceptionality aren't we? Without deciding
8 first whether this is ...
9 PA: We have got to get into the realms of sub-groups for this particular patient it leads you
10 into exceptionality because of the...because he has put in the intermediate prognostic factor.
11 MD: Because it is efficacious...in that group
12 PA: In that one particular group. So he has led us down the path of exceptionality already.
13 IPCO: So it is efficacious.
14 PA: Well that's for us to decide now whether the 11 months versus the 4 months is
15 efficacious.
16 MD: And is it… What journal is it in?
17 PA: New England Journal of Medicine
18 MD: Yes, you said that already
19 PA: Having said that I'm not sure whether the overall survival is in here actually thinking
20 about it. They are broken down by intermediate, poor...[long pause]
21 DN: It's wrong isn't it? It's really wrong these people are coming through here.
22 FD: What's that?
23 MD: This patient needs end of life care
24 FD: Palliative care
25 MD: And they are being denied it… all of these patients that they are sending through.
26 DN: At the end of the day whether this lady receives this treatment or not they are still on
27 dialysis and they will continue to be on dialysis
28 FD: Unless they give them a transplant
29 DN: From a quality of life point of view they are not giving her end of life...
30 MD: Absolutely and this process will be blocking her coming to terms with dying. That is
31 what he is doing to all these people. He is preventing them coming to terms with death and
32 I think that's a real professional issue.
IPCP May 20

Both the MD (line 23) and the DN (line 29) chime in their support of this view, with the MD's comment about "all these patients they are sending through", containing an implied criticism of the referrer (and reflecting a complaint about excessive referrals that came up in our interviews). It is noted that the patient will continue to be on dialysis even if her life is extended (lines 26-27), and that this will result in a poorer quality of life than end-of-life care (line 29). The MD goes further and

moves to criticize the referring consultant, whom she says is preventing patients from "coming to terms with death" (line 31). After this exchange the discussion moves back to the issue of exceptionality, and the exact size of the intermediate prognostic group. After referring to the numbers from the *NEJM* paper the PA says it comprises 55% of 750 renal cell carcinoma patients in the trial. The panel agree that on this basis, together with the AWMSG's previous guidance about the poor cost effectiveness of Sutent in this context, they will deny the funding request. It is unclear how far the normative concerns that surfaced earlier in the discussion affected this decision.

Conclusions

Gilbert and Mulkay (1984), Knorr-Cetina (1981) and Latour and Woolgar (1986) in different ways all show that scientific knowledge is socially produced and contingent on events in the wider social environment. Many of these insights apply to the situated practice of EBM. In the IPC panel, as in scientific work, evidence and facts are actively constructed, with different degrees of certainty attached to particular items of information according to the imputed authority of the source, the magnitude of differences in outcomes for RCT intervention and control groups, the comprehensiveness of findings *vis-a-vis* matters such as overall survival rates, and the consistency of the findings from multiple studies. Latour and Woolgar (1979) show that, once scientists believe an answer has been found, they generally only seek confirmatory data to the extent they think will be necessary to defeat the criticisms of detractors, and in a similar way it can be observed that what counts as sufficient evidence in the IPC context depends on pragmatic judgements about sufficiency. The rigour of review is limited by the ability of a single PA to search for evidence and prepare notes on new referrals within the time constraints of his part-time role, and the capacity of panel members with different degrees of expertise in pharmacology and trials methodology to evaluate his assessments.

The objective character of the empiricist repertoire is compromised in all these ways, but the panel must also adjust to the fact that the central purpose of case discussions is not to fund all patients who

may derive some benefit, but rather to sift out those patients who will not derive sufficient benefit to justify the cost of the drug. The threshold at which costs are deemed excessive rests on a judgement of value rather than science. But because budgetary constraints exist, EBM must incorporate ideas about relative benefit and degree of health gain in relation to cost, which we have argued are addressed through the procedural repertoire. The notion of exceptionality effectively means that only patients who fall within minority subgroups will be approved, but the panel generally makes this determination without explicitly mentioning cost. Cost remains in the background; the finance director claimed in one meeting that the panel had never declined funding on cost grounds. The panel utilises research evidence to exclude the generality of patients who might derive limited benefit by pointing to the clearer benefit found for defined subgroups investigated in the relevant RCTs. This allows the panel to ration the provision of drugs in a way that generally preserves the appearance of neutral, evidence-based decision making.

As data extract 3 above shows, there are times when the operative decision rules produce uncomfortable outcomes and the panel is made to reflect on its procedures. New evidence of efficacy emerges, new NICE guidance may appear and existing guidance may be amended, and political interventions or legal proceedings may over time change panel policy on approval of particular drugs and aspects of its routine practices. For example legal advice given to the LHB in response to the judicial review proceedings brought as our fieldwork came to an end, suggested a need for more careful drafting of decision letters and explicit reference to budgetary pressures that made hard decisions necessary.

To the extent that IPC panels successfully enact a form of EBM, they must also take cognizance of the rationing imperative and various external pressures that enter the discourse of the meetings. Mostly the panel accomplishes this without great drama using the discursive repertoires we have described, combining empiricism with attention to agreed procedures, and allowing sufficient flexibility to manage episodic contingent disturbances. But as we have seen, such disturbances raised

uncomfortable questions and led the panel to reflect on possible changes to its policies and principles, so that over time there are elements of both continuity and change.

The recent reviews in England and Wales both raised questions about how panels use evidence. The English review highlighted problems that arise when little HTA evidence is available, for example, regarding treatments for rare diseases, but the amended guidance (NHS England, 2017b) left the twin decision criteria of clinical effectiveness and exceptionality largely unchanged. New Welsh guidance (NHS Wales, 2017b) followed a different path by identifying "significant clinical benefit" and "reasonable value for money" as key decision criteria. In broad terms the Welsh guidance states that panels are only required to assess difference from the generality of patients (what had been termed exceptionality) when HTA guidelines recommend not to use an intervention. In other cases the main operative criteria should be benefit, assessed though available evidence, and value, based on the incremental cost effectiveness ratio thresholds used by NICE and AWMSG. Under what is now an All-Wales policy, LHB panels continue to be composed mainly of managers and a senior pharmacist, but two lay members have been added. "Evidence based considerations" (see: section 6) continue to feature prominently, but the complexities of IPFR decisions highlighted in the review are reflected in a passage not found in the earlier regional ethical framework.

> "It is also important to acknowledge that in decision making there is not always an automatic "right" answer that can be scientifically reached. A "reasonable" answer or decision therefore has to be reached, though there may be a range of potentially reasonable decisions. This decision is a compromise based on a balance between different value judgements and scientific (evidence-based) input. Those vested with executive authority have to be able to justify, defend and corporately 'live with' such decisions". (NHS Wales, 2017b, para 4.3.4.)

Clearly, Welsh policy makers recognise the practical limitations of evidence-based decision making in panels in which other real-world pressures inevitably intrude. Policy divergence between England and Wales means that controversy will continue about issues such as exceptionality and assessing benefit

in the absence of authoritative HTA guidelines. Empirical studies of how panels make decisions can usefully contribute to this debate.

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Highlights

- Funding high-cost drugs depends on a pragmatic, time-limited review of evidence
- For funding to be approved both efficacy and exceptionality must be found
- Tensions arise when efficacy but not exceptionality is present
- Decision rules change over time due to political intervention and judicial review
- Moral concerns about the value of a few extra months of life may affect decisions