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Warfarin as a materially and digitally informed drug

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Materially and Digitally Informed Drugs

Abstract

This paper explores the material and digital culture of warfarin, one of the most commonly prescribed medications in the world. The paper uses the drug's 60 year history to describe its materiality and use, showing how and why it has become an informed material. Then, three ethnographic cases show where warfarin has produced and is now reproduced by, three types of information: NHS Trust guidelines; genetic codes and the INR (International Normalized Ratio). When a drug becomes so entangled with informational and digital technologies, it becomes reliant on them for its proper and safe use, it can no longer only be an informed material but is a digitally informed material.

Keywords

Digital materiality; Medication; Digital Drugs; Material Culture; Warfarin

Introduction

What do (RS)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one, C₁₉H₁₆O₄, 10442445, a682277 and CID: 54678486 have in common? They are all ways of describing one of the most commonly prescribed drugs in the world: warfarin. In wide use for over 60 years, warfarin is the chief oral anticoagulant (it slows the clotting of the blood) of its kind in use in the UK and it is prescribed as a prophylactic and treatment for multiple conditions: heart disease; stroke, pulmonary embolism, thrombosis (NHS Choices, 2016). It is used by 1% of the UK population and 6% of people over 80 (NHS, 2016). However, despite its widespread use, warfarin is often considered problematic (Pirmohamed, 2006) because it is complex to prescribe, requires careful monitoring and can have life changing consequences if incorrectly administered. This paper is positioned to disrupt the boundaries of medical anthropology and material culture studies. By moving away from drug biographies (Van der Geest, 1996), valuable as they have proved to be, it engages with a growing body of work describing the anthropology of pharmaceutical drugs and medications (Hardon and Sanabria, 2017; Sanabria, 2016; Taylor, 2005).

Building on Bensaude-Vincent and Stengers' (1996) notion of informed materials and Barry's (2015) discussion of the contemporary pharmaceutical industry and the production of chemicals which are agentive and creative, I discuss warfarin, its materiality and use, and how it has become rich in information, materially and digitally. This will be illustrated using three ethnographic moments, where warfarin has produced and is now reproduced by, three types of information: NHS Trust guidelines; genetic codes and INR (International Normalized Ratio) readings. This illustrates the complexity at play between warfarin as an information-rich material and digital technologies. The paper goes on to discuss how this entanglement constructs and is constructed by warfarin in terms of its amenability and resistance to digital technologies. The materiality of the digital meets the materiality of the world configured as machine, architecture, or information and reveals shifting responsibilities and sites of action. The complexity which these assemblages demonstrate reveal how warfarin changes as a medication when it becomes a 'digital drug'.

Informed materials

In their *History of Chemistry*, Bensaude-Vincent and Stengers (1996) introduce the notion of 'informed materials' to describe how the microstructure of chemicals yields up information and how chemicals become co-constructed in this process. They unpick the way chemical research and development has become thought of as an applied science: a service industry. Substances,

materials and information are closely managed and standardized and what constitutes chemical knowledge, facts and information is negotiable and changeable over time, often under the insistence of instrumentation (Bensaude-Vincent and Stengers, 1996: 247). The chemical industry, they argue, produces products that are informed 'in the sense that the material structure becomes richer and richer in information' (1996: 206).

Barry (2015) takes up this notion to think through how the contemporary pharmaceutical industry constructs and designs its products. This is a creative process, where chemicals become pharmaceuticals through design and testing and, in the process accumulate information. The claim is that 'molecules should not be viewed as discrete objects, but as constituted in their relations to complex informational and material environments' (2015: 50). Molecules are often theorised and described as identical and exhibiting identical behaviour. But as Barry points out, molecules and atoms behave differently in different compounds and these in turn behave differently in the laboratory and the body. When a chemical encounters the world it is changed by the process. The chemical becomes transformed through associations with other elements (through reaction or purification), through spatial or environmental configurations (laboratories and factories) or through different physical conditions such as changes in temperature, light or moisture or by being incorporated into further regulatory regimes: a process Barry describes as 'translation'. Brives (2016) describes medications as 'biomedical packages', informed materials located in different environments which cease to be bounded objects because of their interactions with bodies, environments and social constructions. These 'expressive patterns' of information (DeLanda, 2009: 1) produced in different environments require a lot of work to harness, stabilize, replicate and manage on an ongoing basis. They are shaped by social conventions and circulated to produce new information which is simultaneously technical, chemical, experimental, practical and social.

A further claim Bensaude-Vincent and Stengers make is the notion of a chemical coming to 'embody a different notion of matter' because of its ability to give up and reciprocally hold information (1996: 206). This is not simply accretion, but an ontological shift, one which produces a very different kind of material. The work performed on a chemical, say coumarin, results in another, derivative chemical, dicoumarol which is shaped, tested and worked into what is known as warfarin (or warfarin sodium). Warfarin then becomes entangled in a variety of legal, ethical, scientific and pharmaceutical frameworks and emerges as a medication produced in liquid form for intravenous use in hospitals and in oral suspension or packaged as small, dull coloured pills in a variety of dose strengths for prescription only. A complimentary part of this claim is the notion that some objects or materials do more than embody broad societal categories: they exhibit an agency deriving from their microstructure. This is what makes informed materials such an intriguing idea and one which attends to a neglected aspect of material culture studies. It is the chemical agency of drugs which is agential, both because we make it so and because it 'pushes back' as Barad (2007) would have it, from its microstructure. Medications such as warfarin can be dangerous and physically damaging if used in the 'wrong' way. 15-20mg, which is a relatively small amount, could kill a healthy person and those being prescribed the drug could suffer life threatening consequences if their dose is incorrectly given. A pill, sold without its packaging becomes a very different kind of drug and potentially a dangerous and deadly one.

What happens when a data-rich material becomes digital? In order to illustrate this, I start with a history of how warfarin has become an informed material. Then, three ethnographic moments draw in more closely on some of the different kinds of information that constitute the informedness of warfarin and under what conditions. Digital technologies change both the information surrounding the medication and the medication itself in practice. This can be productive in thinking through warfarin's entanglement with digital technologies and the claim that it has become a 'digital drug'.

Warfarin is: 'both dependent on and substantially constituted by multiple digital representations and connections, and whose use and effectiveness is strongly mediated through digital means' (Cornford and Lichtner, 2014).

The data for this paper have been gathered by observations with app developers, patients and within hospital pharmacies and from in-depth interviews, desk research and content analysis, over the course of two years.

Informing warfarin

Warfarin's origin story, as told by Karl Link (1959) and Wardrop and Keeling (2008) informs the context out of which it comes. In the 1920s, American and Canadian farming communities were experiencing extreme rural poverty. As they struggled, they were beset by a series of wet summers, poor harvests, rat infestations and cattle dying mysteriously from internal bleeding. Investigations by Frank Schofield (1924), a vet in Ontario, revealed a link between the dying cattle and the sweet clover present in their poor quality animal feed. The condition became known as Sweet Clover Disease. The moulds *Penicillium nigricans* and *Penicillium jensi*, present in the damp sweet clover (*Melilotus alba* and *Melilotus officinalis*) were oxidising coumarin (responsible for the smell of newly mown hay) into dicoumarol, leading to internal bleeding and the subsequent death of the cattle. Later, Lee Roderick (1929), a scientist at the Agricultural Experimental Station of North Dakota made the link between coumarin and a lack of prothrombin, a clotting factor in the blood, so isolating the cause of the internal bleeding.

Karl Link's team at the laboratory in the Wisconsin Alumni Research Foundation (WARF) worked for 7 years (1933-1940), systematically synthesizing and testing over 150 variations of coumarin. For this, his team developed a new technique: 'in-vitro clotting assay' using plasma from rabbits, developed to guide chemical fractionation of the compounds found in the hay. The most active of these newly produced chemicals, number 42, was named dicoumarol and in 1941, the research funder, WARF, took out a patent on the new chemical (Wardrop and Keeling, 2008). Although dicoumarol was available for medical treatment from 1941, and a flurry of 50 clinical reports were published between 1941-44, Link and others did not consider dicoumarol to be of much benefit for humans, because of its slow action. So, it had little real commercial value until some years later. In 1948, Link was recovering from a lung infection in a rat infested sanatorium and he decided this new chemical might make an effective rat poison. But it was not until an army recruit attempted suicide by rat poison in the early 1950s and was successfully treated, that human use was made widespread (Pirmohamed, 2006).

It requires a significant kind and amount of work for a chemical to be created and developed and then undergo the process of acquiring the competencies (Brives, 2016) which convert it into a therapeutic medicine. Plant derived coumarin, for example, has no effect on blood clotting or vitamin K, it needs to be made to do this. Warfarin's pharmaceutical history (Dickson, 2015) can be traced through the British National Formulary (BNF), which contains all the medications available for prescription in the UK. It reveals how warfarin continues to increase in complexity through data gathered by decades of research studies and evidenced by BNF sections on uses, doses, duration, monitoring, haemorrhage, perioperative anticoagulation, children, hepatic impairment, renal impairment, pregnancy and treatment booklets. Early entries speak to a high 'loading' (induction) dose which was typically set at 30-50mg. However, ongoing research in this area has resulted in reductions and by the 1980s loading doses were typically 10mg. In the NHS Trust involved in this study loading dose is 5mg. Maintenance doses have also been greatly reduced, from typically, 10mg to 2-5mg daily, although this can vary according to individual sensitivity as discussed below.

Similarly, side effects which were described as 'rare' in the mid-20th century rise in number, severity and complexity through current editions. The knowledge of interactions with other medications has also been a matter of concern as this number increases over the years. Warfarin is now so inexpensive to produce that it has lowered the threshold for administration, calculated through a CHADS₂ (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke) score, a point system used to assess medical risk. As a generic, warfarin now costs significantly less than treatment for many conditions (AFA, 2011) and it is increasingly used as a preventative medicine.

The interaction of a (chemical) drug with biological bodies which are not just physical but also informational (Favareau, 2010) creates new information which can be gathered to produce new knowledge (as the case studies below demonstrate). Made practical, information becomes embedded within the material and as the history of warfarin shows, the process of 'informing' is reciprocal, active and ongoing, the material both shaping and describing the social relations contained within it. Medications are dependent on multiple sources of information to mediate their use: make it usable and safe. Information on the pack commands: take 1 once a day and when: with food. The information sheet inside the packet provides information on side effects, when not to take the medication and when to revisit the doctor if no change in symptoms occurs. Details on manufacturer and barcodes ensure safe passage through the supply chain and are just some of the other sources of information the packet provides. The physical appearance of the medication encodes important information. Tablets are colour coded for easy identification. Most patients carry doses of 1mg (brown tablets), 3mg (blue) and 5mg (pink), out of which any dose can be made up as required.

Warfarin as a digital material

Digital technologies have reformed almost every aspect of medical practice in the UK with the introduction of: nanotechnologies; robotics; tissue engineering; machines; databases; Internet of Things; electronic prescribing; protocols; big data. Medical information has to exhibit certain qualities in practice to be made digital (digitized): accessibility; accuracy and reliability; digestibility; interactivity and directability. It needs to be given, received, stored and shared although as the case studies reveal, these are ideal conditions which are not met in every case. From its chemical identity ((RS)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one and C₁₉H₁₆O₄) warfarin has increasingly developed a range of digital identities as it becomes entangled with databases where it lives as: CID: 54678486 in PubChem, a database of chemicals and their actions; as 10442445 in ChemSpider, the Royal Society of Chemistry's database or a682277 in MedlinePlus, the US National Library of Medicine. These provide further information and knowledge about warfarin as a technical, chemical and biological material. In turn, data is changed by this process and it is possible to generate data entirely digitally (digitalization). *In silico* testing, for example, involves digital tools which invent and test virtual digital compounds and materials which have never been synthesised in a laboratory. Ironically, these 'computational experiments are closer to life as lived than traditional laboratory experiments as they are likely to be based on data derived from trials on living bodies, whereas laboratory experiments are conducted in standard solutions' (Barry, 2015: 63).

Digital technologies have become an increasingly "constitutive part of what makes us human' (Miller and Horst, 2012: 4). They are also increasingly constitutive of digital patients (Lupton, 2014b) who use smartphone apps for diagnosis (Lupton and Jutel, 2015), medication and appointment reminders. People who take warfarin are swapping their paper Oral Anticoagulation Therapy 'yellow books', used for recording and reporting INR readings, with digital apps. Home testing has taken off with the introduction of hand-held digital testing machines, email and SMS

reporting. Clinicians too, take on increasingly digital identities (Lupton, 2014a), using skype for consultations and dose calculating algorithms for warfarin prescription. They not only recommend apps but are increasingly involved in using, designing and publishing them.

The three ethnographic moments that follow present times where warfarin can be seen to be an informed material and a digital material. This is more than a simple split between the drug as a material object and its semantic or visual representations which may be described as digital or informational (barcodes, codes in digital systems, algorithms to calculate dose etc.). Chemicals and the compounds they form 'give up' information which is reworked and shaped into data that digital technologies can store, rework, reorder, transfer and these in turn reshape the nature of the drug. Each case describes a different source of information: blood clotting factors; genetic material and NHS guidelines and illustrate how warfarin is informed by these and how that informedness is produced digitally. In the first, digital environments produce new knowledge about what the body is 'doing' with warfarin as a patient home tests. As the warfarin consumer enjoys the process of becoming a 'good warfarin patient', s/he also reveals how this digital terrain is uneven and interrupted. The second case shows how warfarin interacts with the materiality of the body in the form of genetic expression, 'surfacing' (Taylor, 2005) information which can be digitised in terms which produce 'sensitivity'. Ongoing research projects render warfarin more and more data-heavy, but simultaneously more and more individualistic. The third case demonstrates how a prescribing support app draws together the NHS Trust's guidelines to produce a protocol for the initiation and stabilization of warfarin prescribing. This results in changes of the location of information, calculation, patient interaction and the nature of the drug. As digital actors, patients, clinicians and researchers all contribute to warfarin as a digital drug and all are constructed by its digital nature.

Warfarin home testing

Harry inserts a test strip into the hand-held testing machine and it beeps to confirm contact. He pushes the very fine, sharp needle into the pen. He draws the blood to the end of his middle fingertip, a process he calls milking, because it mimics the action of milking a cow. When he judges the finger ready, he uses the pen to draw a large drop of blood which he transfers to a channel on the end of the testing strip. The machine beeps again to confirm the action and displays a number which Harry notes in his 'yellow book,' tucking it back into the kit bag for next time. He is pleased with the result because he is within range.

Warfarin is a vitamin K antagonist (VKA). Because it is chemically similar to vitamin K, it interjects in the chemical pathway, a series of enzyme-controlled chemical reactions that produce blood clotting, by interfering with the vitamin's action. Therefore, testing the rate at which Harry's blood clots is a way of monitoring how much warfarin he requires. This information is vital, because too high a dose of warfarin and complications such as blood clots, stroke and heart attacks can result. If too little is taken, bleeding events including internal bleeding become a risk. People usually cannot tell whether they have over or under medicated until a potentially life changing event occurs. The test result is standardized and expressed as the International Normalized Ratio (INR). This creates a 'calculative infrastructure ... a field of social action, making some relations between people, institutions, and materials possible' (Nafus, 2014: 208). The INR becomes the language through which patients and practitioners communicate, with 1 recognised as the standard and patients aim to stay 'within range' of 2 to 3 by altering the amount of warfarin they take. The INR is datafied in a yellow booklet issued with the medication and patients are encouraged to keep this information, although as many report, their physicians are not interested in the historical data. They concentrate only on the current readings.

Staying within range is not as simple as adjusting medication in relation to blood chemistry, however. In the same way that warfarin interferes with vitamin K in blood clotting, Vitamin K in common foods interfere with warfarin's action. In addition, alcohol, smoking, exercise, general health status, weight, age and other medications significantly affect the drug. In this respect, warfarin, although standardized in the tablet and through the INR, becomes highly individualistic, as information about the body/drug assemblage (Gagnon and Holmes, 2016) is made visible through the blood. Blood has long been an anthropological concern, deeply implicated in studies of politics, race, symbolism, kinship and medicine, leading to conclusions that blood contains the capacity to "reveal the truth" – morally, personally, politically, and medically' (Carsten, 2013: S1). Harry, as many other people who take warfarin do, works hard to align his body's chemistry through the INR numbers by balancing his daily activities and food intake, trying to develop a 'steady state'. This is accomplished through the difficult and continuous work of regularising lifestyle, exercise, alcohol intake and diet, including reducing vitamin K rich foods.

Lifestyle and food intake may still not be enough to contain the effects of warfarin, due in part to the medication's narrow therapeutic index, where a small amount of medication can produce a large effect on blood chemistry and a high level of variation between patients. Taking only a small amount of incorrect medication can result in out of control INRs and a typical maintenance dose is set between 2-5mg per day, although some respondents require up to 10-11mg per day. People who have had emergency vitamin K therapy after life threatening INR imbalance develop a tolerance to warfarin, requiring high doses afterwards.

Digital testing produces consequences for the medical system and the patient, even if this 'technogeography of care' (Oudshoorn, 2011: 124) is currently uneven. Before buying his testing machine, Harry had to go to the clinic, wait in line, have his blood taken, wait again for the results and be told by the clinician whether his warfarin prescription required adjustment. He had to take half a day away from his job to do this, so he is delighted to be able to test his INR at home, at his convenience. Another respondent who travels frequently reports that it is often difficult to arrange clinic appointments or to find a walk in clinic abroad. He likes home testing too. Shifting the location of testing from hospitals and clinic means that the home (Exley and Allen, 2007) or potentially anywhere becomes a testing place. However, home testing is expensive. Harry's machine is not currently available on the NHS and cost him £300. The test strips are an additional cost and are often 'a battle' to have prescribed (interviews and pers comms), and this varies from one health authority to another. But to Harry, the cost is worth it because it represents a freedom from clinic visits and the ability to take control of his health.

Home testing is not suitable for everyone nor can everyone afford this semi-private healthcare. Despite the wider NHS (2014) recognition that patient self-management through home testing can lead to a significant improvement in the quality of oral anticoagulation (Garcia-Alamino, 2010), increased quality of life for the patient and financial savings for the NHS, medical practitioners worry about enabling patients to self-test. This is revealed through anxiety over the patient's ability to remember and note their reading accurately or in the machine itself and its ability to calculate correctly. At hospital visits and through respondents, I hear of doctors asking patients to bring in their machines for calibration 'just to make sure' they are accurate. Harry concurs, saying his clinic also asks him to do this and during one interview, he becomes curious about the precision and accuracy of these tests.

After looking through the printed instruction leaflets, which are numerous, we turn to the manufacturer's website for help. There seems to be some confusion about where the locus of activity lies. Finally, we phone the manufacturer and learn that the machine itself does not do any

calibration, it is the test strips that perform the work. Each test machine and each batch of test strips possess a number and a unique barcode. Every time a test strip is inserted, the machine verifies the match (and 'beeps'). So 'testing the machine' is in fact testing to make sure the machine recognises that one batch of strips matches its equivalent chip. All the testing is done in the strip; the machine merely verifies the strips and displays the result. The machine can store results but it does not transfer the information to computer or Harry's clinician, although he would like it to. He notes his test result and either emails or rings his clinic, leaves a message and then waits for someone to contact him with any required dose adjustment. The clinic may record his test on the DAWN computer system discussed in the next section, if they use it. Harry does not know which computer systems they use, where the information travels to, who deals with it or how it is stored or used when it leaves him.

Home testing refocuses and enables patient involvement, engagement with and responsibility for medicines and self-care. For the less seriously ill patient, home testing can also enable some experimentation. One respondent recounted his experiments with alcohol because he was curious what it would do to his INR readings. On different nights he drank different amounts of wine and measured his INR at home. Harry and other respondents talk about a sense of freedom, control and agency over their health. Some respondents now replace their yellow books with smartphone apps to collect their INR readings, record daily doses, other medications and clinical appointments although Harry does not do this. He does not engage with other digital resources. He does not use apps, for example, nor does he go into online forums or social media. He does set digital medication reminders because, as part of the process of regularising warfarin and the body, warfarin has to be taken at the same time every day. Unlike users of social media sites who increase their knowledge through giving and sharing information, Harry actively withdraws from this kind of contact in order to regain some measure of normalcy.

Genetic research

'What we found is that these three genetic markers which were used to predict dose in the European population were not accurate at predicting dose in the Gujarati Indian population. When a similar study was carried out in America, in the African American population, they came up with similar results' (interview, Dr Harsh Sheth, Postdoctoral Research Associate).

Research into the medical applications of warfarin has been ongoing since the 1940s. Subjects tended to be white, male, young and healthy and this produced a particular biological body, the results from which were then unproblematically transferred to other groups such as women, older people, people with multiple or long term conditions and ultimately, to all global populations. Genomics, too has been employed in the project of unifying humans, through the homogenisation of the genetic code and determined as information passing through time where the analogical genetic code produces the bodies that replicate its production and form a 'line of communication' with generations past and future (Hoffmeyer, 2010: 619). However, the genetic code is now understood to be changing, constantly under revision as it replicates and produces new proteins and cells. Each is unique, increasing in variation as it ages; producing ever-changing environments for drugs to interact with. It is also now understood that over 50% of the variation in warfarin dose requirements comes from the condition of the body in combination with genetic factors. These are described as genetic polymorphisms in CYP2C9 and VKORC1 and worldwide, research shows that there is a high interpatient variability of up to 40 fold between different populations (Sconce et al., 2005).

However, currently prescribing clinicians cannot routinely take genetic variance into account when prescribing. They consider the lifestyle and physical body of the patient; including the medical

conditions they have plus age and body surface (a calculation derived from height and weight). Currently, calculating the correct dose is achieved largely through 'trial and error' over many weeks leaving the patient at risk from over or under prescription until a stabilized maintenance dose is achieved (NHS, 2016: 12). This also means frequent visits to the doctor or hospital clinic for blood tests, a process which can be lengthy and expensive for the patient and clinic. At the Institute of Genetic Medicine at Newcastle University, Harsh explains how he contributes to solving this expensive, inconvenient and potentially unsafe 'trial and error' approach. The Institute has a long history of research into warfarin and other medications and was involved with the production of an algorithm for warfarin prescription, released in 2009. Harsh and his team conduct Genome Wide Association Studies (GWAS), trying to determine if and where there might be a genetic association to warfarin. GWAS are a type of case control study (Sheth et al., 2015) which is: 'a mathematical way to calculate whether a [genetic] marker is associated with warfarin response' (interview).

Genomics is one of a group of 'omic' technologies facilitated through digital technologies and proliferating since the sequencing of the genome. These omics generate a high throughput of data, enable that data to be individualised and allow data derived from different sources to combine to predict which genetic markers may be associated with warfarin uptake and metabolism (pharmacogenetics). Harsh's GWAS studies gather two kinds of data from two groups of patients. First, patients are divided into a case group which consists of people requiring a very low dose of warfarin; less than 1.5mg per day and the control group, which contains patients who are not as sensitive and typically take 3mg or more per day. Data is gathered on the genetic codes of these research participants and from questionnaires on a wide selection of physical and lifestyle data: age, height, weight, alcohol, and tobacco and medication consumption. This is sorted and a digitally facilitated statistical analysis carried out.

The genetic code becomes a primary source of information for Harsh, supplemented and made meaningful with the addition of physical and lifestyle data from research participants. This is used to describe the frequencies of genetic markers and these are compared between the two groups. If genetic markers occur at a higher frequency across one group compared to the other then it can be said that the particular marker is most likely to be associated with warfarin dose. As Harsh's research demonstrates, isolating genes and groups of genes responsible for rare or serious diseases produces knowledge in the form of 'biomarkers' in process of 'surfacing' (Taylor, 2005). This is hastening the turn to personalised medicine which promises a shift from 'one size fits all' to a 'new taxonomy of medicine based on underlying cause and personal response' (NHS, 2016: 15). In this case, the genetic code, combined with biographical data, produces actionable knowledge about warfarin metabolism and risk.

The study of genomics now depends on digital technologies to render the body intelligible in ways which make population group visible within warfarin prescribing practices. This new competency (Brives, 2016) is on the verge of being applied clinically, through handheld testing devices (Harsh, interview). These can be used to test for warfarin sensitivity using biomarkers. The device relies on disposable cartridges which do the testing work, much like Harry's testing strips. Harsh talks about how the application of a one-time test for warfarin sensitivity will make prediction of dose more accurate, cheaper, able to be done anywhere and quicker: 20 minutes versus the current 3-7 days. However, unlike Harry's testing machine, the data transfers to the clinician's computer automatically.

A decision support app for hospital prescribers

'Warfarin has always been a hard thing to deal with when it comes to technology' (interview, Mary, pharmacist).

Adia, the Consultant Pharmacist for Anticoagulation in a large Hospital Trust is dedicated to ensuring the ongoing improvement of the safe prescription and consumption of warfarin. She describes how the kind of research Harsh conducts comes together to produce an area of concern round warfarin, defining the drug as 'risky' and as a site for intervention. Of immediate concern, warfarin is one of the top three drugs associated with hospital admissions she explains, especially in the elderly population. Many of these admissions are readmissions due to some patient's inability to control their INRs and as such they are regarded as preventable (McNab et al., 2015). The stakes are further heightened because warfarin is one of the drugs most associated with fatal medication errors (Hart-George, 2013) and as a hospital pharmacy poster warns: 15% of all doctor's prescriptions contain errors. As most hospital prescribing is primarily done by junior doctors, the posters urge pharmacists to check and double check each prescription. This pharmaceutical gaze is 'defined by objects (medicines)' and the 'ability to see the properties of medicines' and understand them in specific ways related to individuals and their illnesses (2005: 78). Doctors may prescribe what they like, but pharmacists ensure the safety of prescribed medications (Dickson, 2015). As another pharmacist says simply but firmly, 'we control the drugs'.

Adia explains how, unlike many other medications, warfarin is difficult to prescribe safely. Not only is it prescribed in different doses for multiple conditions, the patient may have other serious illnesses e.g.: liver disease or diabetes and drugs they take for these can produce complex interactions, combining to affect warfarin sensitivity. As we have seen, genetic sensitivity, condition of the body, lifestyle and a narrow therapeutic index have to be assessed quickly and efficiently by the prescriber to avoid all the serious risks over and under prescribing involves. In addition, warfarin has a slow onset of action, which means it can take up to three days to reach full effect and a slow half-life, taking up to five days to leave the body. This makes it particularly challenging to manage in the hospital setting where patients who become medically non-critical and who could be moved home, still require daily monitoring in a clinical environment to achieve a stable dosing regimen. The two timescales: one dictated by drug metabolism, the other involving bed turnover are at odds with the smooth and quick discharge of the patient. Adia was interested in Harsh's work for this reason.

The digital life of warfarin in a hospital is complex and this complexity is written into the National Institute for Health and Care Excellence (NICE) guidelines, to which all NHS Hospital Trusts in the UK are expected to adhere. This might suggest a uniformity of care across settings, but significant variation has been noted (Stewart et al., 2015). Each Trust develops and implements its own protocols and workflows round warfarin initiation and stabilisation. While not all Trusts use digital reporting and prescribing aids, in Adia's Hospital Trust a dedicated system, DAWN anticoagulation software is in use. In DAWN, each patient has their own page into which data can be entered, including: patient medical history; treatment plans and notes; details about carers, family, and appointment non-attendance. There is a section for a patient photograph although this is usually left blank (consenting and recognisability issues, short inpatient stay etc.). DAWN uses an algorithm to calculate warfarin dose, however it does not link to this Trust's protocols or workflows so rendering the dosing algorithm inactive.

Adia updated the Trust's warfarin dosing guidelines in 2015, concentrating on the protocol for inpatients. At that time, she used another Trust's percentage dose adjustments which consisted of a chart of all the dose adjustments required by a prescriber, when a patient's INR was out of range. Using the patient's current INR reading and the target INR, the dose adjustment was calculated. These calculations were produced in Excel spreadsheets. She double checked them herself as did another pharmacist, Mary. They ended up as 'reams and reams of tables for patients on doses

from 1mg to 10mg' (Adia). However, these percentage adjustments were perceived by the Trust's Drugs and Therapeutics Committee to be inaccessible and they suggested an app: 'the user could input what the patient's INR is, what dose they are on and then it could come out with the answer in this table just for that specific thing ... that would be very useful' (Adia).

Initially this looks like an easy example of digitization: converting non-digital information (dose alteration calculations) into digital information, without a change in that information. 'It's not as easy as just cut-and-paste, or you know, a table into a user-friendly format' (Adia). The app reorganises the information and incorporates the dose alterations into the Trust's protocols. It also provides the 'opportunity to just be a little bit more interactive with your guidance' (Adia). It leads the user through a series of stages of the protocol, asking questions and drawing attention to the way the patient responds, creating a pathway through the information and guidelines. The way the information is produced in excel spreadsheets and with calculators is a digital process but because the app is the last step, presenting the information it is this which is described by respondents as 'digital' the other steps having been normalized or black-boxed during the process.

The smartphone start-up screen shouts: 'Warning: THIS GUIDANCE DOES NOT NEGATE THE NEED TO USE CLINICAL JUDGEMENT IN MANAGING EACH PATIENT'

The warning draws together a number of ideas about app users and the clinical situation. Firstly, it is not simply a legal reminder that the app developers are not responsible for any mistake that is made within the hospital setting, the warning mediates between the inexperience that the prescriber might have in navigating such a complex decision, where drug action on the individual, as indicated by the final words of the warning 'each patient' cannot always be reduced to a rational calculation or algorithm. The body/drug assemblage is so complex and the stakes of inaccurate medication so high, that the clinician is put and kept in charge of the treatment pathway and the vital calculation of dose initiation and adjustment. Harry, from case study one, for example bemoans how he could easily calculate his own dose, using an app such as this one.

The rate of informedness warfarin acquires from research means that it is constantly moving, becoming richer in data. NICE guidelines are informed by continually updated research from sources such as: The British Committee for Standards in Haematology; The Information Centre for Health and Social Care; the UK heart valve registry (UKHVR); the Office for National Statistics and the National Patient Safety Agency. Trust guidelines and protocols are constantly under review. This means that the app, cannot be a static product, complete at the point of use. It becomes a constantly updated technological process. 'And this is when we realised we probably have to build the app in a way that in the future, specific end users could change and alter - update if you like' (Mary, pharmacist).

While the app achieves many things, it does not reconfigure interconnectivity between computer systems. While it is fully integrated with Trust guidelines, it is not (yet) available on this Trust's computers and is only accessible via smartphone. The app remains isolated from hospital systems and is not linked to the electronic prescribing system or to the DAWN system available on the computer carts that doctors take on their ward rounds in this hospital Trust. However, the app does solve some problems regarding speed, readability and the navigation of complex protocols and dosing adjustments. It also neatly bypasses the problems of NHS computer shortage and additional money for prescriber support and training because prescribers generally own and are willing to use their own phones.

Conclusion

Products of modernist industrial processes, pharmaceuticals do not just exist, waiting to be 'discovered'. They are designed, produced and tested for properties in processes where their microstructures yield information, producing 'informed materials' (Bensaude-Vincent and Stengers, 1996). As warfarin's history shows, it has been an informed material since dicoumarol production in the 1940s, holding increasingly complex patterns of action and use. It has been informed through Carl Link's storytelling, through chemical analysis, drug testing and since the 1990s, digital and genetic testing. Harsh's work contributes to warfarin's complexity and informedness, as does Adia's. While warfarin has always behaved differently in different bodies, more is known about this now and as a digital drug, it is enabled to be further targeted to the individual patient in terms of diet, lifestyle and genetics.

However, informed materiality can be problematic. The complexity, kind and volume of information on warfarin compels Hospitals Trusts to implement large and detailed protocols in order to manage the drug safely. The dosing app, loaded with these protocols and tables of dose adjustments, organise the ways in which clinicians become better prescribers. The NHS imagines a connected digital future where all departments and their information link. In reality, these digital moments remain unconnected. Information does not flow. The dosing app is not connected to any other hospital system, especially DAWN. Harry's testing machine remains uncommunicative and isolated from his anticoagulation clinic. The testing machine materialises a tension between patients who wish to be independent and clinicians who need to ensure their safety.

A lot of work goes into harnessing the chemical agency of warfarin and its interaction with bodies (regulatory, legal, chemical, medicinal, pharmaceutical, social, research, commercial) and this makes it increasingly richer in information. Immersed now in digital technologies, it has become dependent on digital data, testing, analysis and machines for its safe production, prescription and consumption and those digital technologies in turn reorder and change the information that warfarin creates and assembles.

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