Too Much Medicine

Using interdisciplinary research to explore how to solve the problem





Too Much Medicine

Wednesday, April 19, 2017

8:00am to 9:00am	Registration & Coffee
9:00am to 9:30am	Welcome to Kellogg College (Jonathan Michie) Conference Introduction (Jeremy Howick)
10:00am to 11:00am Chair: Jeremy Howick	Keynote Address : Lisa Schwartz and Steve Woloshin. "Too many tests, too much medicine, and what we can do about it"
11:00am to 11:30am	Break
11:30am to 1:00 pm Chair: Jeremy Howick	 Bennett Holman "Combining philosophy with qualitative methods to evaluate patient groups' views on Flibanserin and female sexual dysfunction" Wendy Rogers and Mary Walker. "Précising definitions as a way to combat overdiagnosis" Richard Stevens et al. "Do concepts of disease apply to "chronic kidney disease"?
1:00 pm to 2:00 pm	Lunch
2:00 pm to 3:00 pm Chair: Jeremy Howick	Keynote address : Alexander Bird "Too Many Hypotheses? Understanding the replication crisis in medicine and psychology"
3:00 pm to 4:30 pm (parallel sessions) Chair: Susanne Uusitalo	 Luciana Garbayo. "Medical Guidelines Multi-Experts" Huw Llewelyn "Over-diagnosis from the perspective of a medical practitioner and teacher" Saloni de Souza "Too Much of a Good Thing?"
3:00 pm to 4:30 pm (parallel sessions) Chair: Jonathan Livingstone-Banks	 Jonathan Fuller. "Simple Extrapolation and Overtreatment in Medicine" Richard Holton and Zoe Fritz. "Trust and Treatment" Margaret Steele "Having Obesity versus Being Fat: Philosophical problems with defining obesity as a disease."
4:30 pm to 5:30 pm	Wine Reception & networking event

Thursday, April 20, 2017

9:00am to 10:15am	Keynote Address: Jeffrey Aronson. "Too much of Everything"
10:15am to	Break

10:45am	
10:45am to 12:15 pm (parallel sessions) Chair: Charlotte Albury	 Michael de Barra. "Reporting Bias Inflates the Reputation of Medical Treatments: A Comparison of Outcomes in Clinical Trials and Online Product Reviews" Michael Wilde. "Too Many Carcinogens: Mechanistic Evidence and the International Agency for Research on Cancer" Jonathan Livingstone-Banks "The Case for a Meta-Nosological Survey of Disease Classificational Practices in Modern Mainstream Medicine"
10:45am to 12:15 pm (parallel sessions) Chair: Susanne Uusitalo	 Petra Makela "Collective performativity in nursing home to hospital transitions" Julian Treadwell. "Why General Practitioners care about "Too Much Medicine", and their role in addressing it." Lynette Reid "Objectivity, subjectivity, and harm in cancer overdiagnosis"
12:15 pm to 1:15 pm	Lunch
1:15 pm to 2:00 pm Chair: Susanne Uusitalo	Keynote address : Jeremy Howick "The emerging discipline of empirical philosophy and how it can help solve the problem with too much medicine"
2:00 pm to 2:30 pm Chair: Charlotte Albury	Iain Chalmers, Selena Ryan-Vig, Sarah Pannell, Astrid Austvoll- Dahlgren, and Andy Oxman "Informed Health Choices Key Concepts and their application"
2:30 pm to 3:00 pm	Short tea break
3:00 pm to 4:30 pm Chair: Jeremy Howick	Open discussion: "Is medicine relevant to philosophy?"/ "Can philosophy help solve the problem of too much medicine?" And future research agenda.
4:30 pm to 5:00 pm	Closing remarks: Jeremy Howick

Keynote speakers & Abstracts

Dr. Lisa Schwartz and Dr. Steven Woloshin



Dr Schwartz and Dr Woloshin are professors of medicine, and of community & family medicine at the Dartmouth Institute for Health Policy and Clinical Practice. They are also co-directors, of the 'Medicine in the Media' programme. Their collaborative work has 2 main approaches: improving the quality of messages presenting health information to people, and preparing audiences to make sense of the messages they Ther main focus is receive. on the communication of medical statistics and information about the benefits and harms of screening and prescription drugs.

Professors Schwartz and Woloshin will discuss their decades of work on the problem of Overdiagnosis, an important cause of "too much medicine": what are the different forms and drivers, what are the health consequences, and what we can do to limit harm.

Prof. Alexander Bird's research is in the metaphysics and epistemology of science and medicine. His book *Nature's Metaphysics* argued for a dispositional essentialist account of natural properties and necessitarianism about the laws of nature. He is now working on a book about scientific knowledge.

Recent 'meta-research' has shown that up to half of medical and psychological findings cannot be replicated. In this plenary lecture Professor Alexander Bird will combine philosophical and epidemiological considerations to argue that the problem with failure to replicate arises (in large part) because too many hypotheses. He will also suggest ways to solve the problem. Prof. Alexander Bird



Dr. Jeffrey Aronson



Dr Aronson is a consultant physician and clinical phamacologist. His research interests include the classifying, detecting, and reporting of adverse reactions to drugs and innovation in drug therapy. He is a member of the Oxford University Hospital Trust's Drug and Therapeutics Committee, advising on the Trust's use of medications, a member of the Advisory Board of the British National Formulary, and President Emeritus of the British Pharmacological Society.

In his talk, Professor Aronson will discuss his decades of research in clinical pharmacology to illustrate the problems with too much diagnosis, too much medicine, and too much of everything many other things...

Dr. Jeremy Howick

Dr. Howick is a senior research in the Nuffield Department of Primary Care, Univeristy of Oxford, and director of the Oxford empathy programme. Dr. Howick's research draws on his interdisciplinary training as a philosopher of science and clinical epidemiologist. He has two related areas of interest: Evidence-Based Medicine (EBM) and Philosophy of medicine. His work in EBM cumulated in a book ('The Philosophy of Evidence-Based Medicine') and a tool for gauging Levels of Evidence. Dr. Howick's philosophical research focuses on the justification for EBM 'hierarchies', the evidential role of mechanisms and expertise, and the ethics of placebos in routine practice and clinical trials.

Ancient philosophers aimed to improve their lives, their society, and science. Contemporary philosophy often appears divorced from practical considerations. Yet recent research in the philosophy of medicine suggests that philosophy of medicine and medicine itself can be related. In this overview, Dr. Howick argues with examples that some medical (scientific) questions require philosophy, and vice versa. He supports his argument with three case studies:

(1) The ethics and epistemology of placebo treatments in clinical practice.

(2) Looking at the difference between randomized trials and observational studies: dissolving the 'paradox of effectiveness'.(3) Evaluating the health benefits of empathy and expectations: when does hope become deception?

He will reply to the potential objection that philosophy cannot be practical.



Conference Venue Kellogg College

62 Banbury Rd, Oxford OX2 6PN, see Google Maps here:





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·Water Eaton, north of Oxford on the A4260 approach to Oxford.

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MacDonald Randolph Hotel, Beaumont Street, Oxford, OX1 2LN Tel: 01865 256 400 Check-in from 2pm Breakfast served in the restaurant 7-10am Check-out time by 11am Limited parking is available on site, charged at £26.50 per night



Mercure Eastgate, 73 High Street, Oxford, OX1 4BE Tel: 01242 307 801 Check-in from 2pm Breakfast served in High Table Brasserie and Bar from 6.30-9.30am Check-out by midday Limited parking on site, charged at £15 per night



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NUFFIELD DEPARTMENT OF **PRIMARY CARE** HEALTH SCIENCES Medical Sciences Division



Parallel session abstracts

Garbayo, Luciana

Medical Guidelines Multi-Experts Multi-Criteria Decision-Making Disagreement Problem: Interdisciplinary Epistemic and Ethical Analyses of Knowledge Norms in the Breast Cancer Screening Overdiagnosis Debate

Managing medical uncertainty and disagreement on overdiagnosis in medicaldecision- making requires tackling legitimate expert disagreement on medical guidelines among different scientific consensus of medical specialties under multiple criteria. The case of the multi-experts multi-criteria disagreement in breast cancer screening guidelines (USPSTF, ACOG) exemplifies the need for the development of powerful interdisciplinary approaches that explore both the philosophical understanding of knowledge norms, epistemic peer disagreement, and overall ethical constraints in medicine, as well as the scientific understanding of medical decision-sciences and data management, for reducing overdiagnosis uncertainty in a patient-centered outcomes perspective. In this investigation we provide a cross-disciplinary modeling framework integrating philosophy of medicine, medical decision sciences and computer science for modeling and analyzing disagreement in breast cancer screening as a multi-expert multicriteria decision-making (MEMCDM) problem. Through epistemic disagreement analyses of a set of interdisciplinary annotated breast cancer screening guidelines and background literature thereof we consider the contributions of an epistemology of disagreement to the epistemic clarification of overdiagnosis problem as a peer disagreement problem. These analyses address both knowledge norms for peer-topeer belief, constraints to knowledge justification and norms for action, further constrained by ethical considerations of obligation under a patient-centered perspective in the breast cancer screening debate.

Reid, Lynette

Objectivity, subjectivity, and harm in cancer overdiagnosis

In diagnostic reasoning, clinicians integrate diverse kinds of information. Many believe that including subjective and functional criteria in disease definition facilitates harmful medicalization. Overdiagnosis in cancer screening, by contrast, arises from an excessive confidence in the value of objectivity for clinical reasoning, in abstraction from whether that objective information can decide important clinical questions (I have argued elsewhere). Clinicians distinguish statistical from clinical significance in statistical evidence; likewise, I argue, we must distinguish clinical utility from accuracy in evaluating claims for improvements in diagnostic testing. I analyze the transition from film to digital mammography and tomosynthesis as examples in which greater accuracy in testing fails to address the relevant uncertainties in clinical decision-making. Is it sometimes better to reason from fuzzy data? In this paper I discuss situations in which fuzzy data may be preferable, and the ethical concerns that would arise from such a preference—in particular, could we be justified in exposing patients to variation in diagnostic practice in order to reduce overdiagnosis and overtreatment? As an example, I evaluate the current move to collapse the distinction between CIN 2 and 3 in diagnostic testing for cervical cancer screening.

Wendy Rogers and Mary Walker

Précising definitions as a way to combat overdiagnosis

Roughly, overdiagnosis (ODx) occurs when people are harmed rather than benefitted by being diagnosed with a condition, because, in their case, the condition is not a harmful case of disease. Overdiagnosed patients are not benefitted and may be harmed in various ways. ODx is a theoretical as well as a practical problem as it relates to definitions of disease. Elsewhere we argue that disease is a vague concept, and that this vagueness may contribute to ODx. In response, we are developing a stipulative or précising definition of disease, aimed at decreasing or preventing ODx, by distinguishing cases where it would be beneficial to identify (and treat) the condition from those where diagnosis is likely to be overdiagnosis. We call this précising definition "diseaseODx". A first definition of diseaseODx is that X is a diseaseODx iff there is dysfunction that has a significant risk of causing severe harm. In this paper we flesh out this definition drawing on a Feinbergian account of comparative harm, and examining the conditions under which it may be ethical to impose levels of risk. We then test the utility of this approach using the examples of osteoporosis and melanoma, both of which are currently overdiagnosed.

Holman, Bennett

Combining philosophy with qualitative methods to evaluate patient groups' views on Flibanserin and female sexual dysfunction

Evaluating a case to determine whether it is an example of overtreatment frequently trades on values: "Which side effects are important enough to include in any measurement of harm? Are some side effects more important than others? Who should decide—patients, clinicians, or researchers? And what if they disagree?"

(Carter et al. 2015). In an effort to deal with just this issue the FDA created the patient focus drug program. Combining philosophy with qualitative methods from the social sciences, our research first examines the October 2014 patient meeting for Flibanserin and female sexual dysfunction. We show that industry-funded participants presented a unified message that was almost completely distinct from other participants. We argue that this process can be understood as an example of a "looping effect" (i.e. women have internalized the industry's narrative which now genuinely structures their experience). Setting this case in context of broader efforts by industry to shape the experience of patient groups, we argue that: At best this significantly complicates efforts to incorporate patient values into risk/benefit judgments and at worst, it belies the presupposition that patient interests are an objective, immutable, and knowable factor to be incorporated into medical decision making and regulatory decisions.

Richard Holton and Zoe Fritz

Trust and Treatment

What is the connection between the treatment a patient is offered and the trust that they have in their doctor? We suggest that sometimes treatment may be a way of building trust; but that sometimes it may be a substitute for it, and this is one of the factors leading to over-treatment. We examine the nature of the trusting relationship between doctor and patient, and at how various factors affect it, including (i) the presention of a diagnosis, especially a differential diagnosis (ii) questioning of the doctor by the patient and (iii) treatment and non-treatment decisions. We argue that if we are to avoid using treatment as a substitute for trust we need to think of building trust as an on-going two-place relationship between patient and doctor (or, more broadly, between patient, family, and medical team).

Wilde, Michael

Too Many Carcinogens: Mechanistic Evidence and the International Agency for Research on Cancer

The aim of the International Agency for Research on Cancer (IARC) is to evaluate the strength of the available evidence concerning whether a particular exposure is carcinogenic to humans. The overall evaluation may be informed by a variety of evidence, including epidemiological studies, cancer bioassays, and mechanistic and other relevant data (IARC, 2015). However, in some cases, the evidence from epidemiological studies alone is taken to be sufficient to establish carcinogenicity. This practice has received some criticism from philosophers of science. In particular, Bert Leuridan and Erik Weber (2011) have argued that there is never sufficient epidemiological evidence for carcinogenicity because this evidence comes only from observational studies, which do not sufficiently rule out the possibility of confounding. As a result, they maintain that this practice is likely to result in false positives, that is, exposures being incorrectly classified as carcinogenic to humans. Loosely speaking, the practice results in too many carcinogens. In order to better avoid false positives, Leuridan andWeber maintain that '[m]echanistic evidence should also be used to better exclude the possibility of confounding in individual epidemiological studies' (2011: 99). Against this, I argue that in some cases the epidemiological evidence alone is sufficient to establish carcinogenicity. In particular, in the recent evaluation of processed meat as carcinogenic, the high-quality epidemiological data established consistent associations between processed meat and colorectal cancer across diverse populations in a way that sufficiently ruled out the possibility of confounding (cf. Bouvard et al. (2015: 1599)). This provides a qualified defence of the practice of IARC.

Makela, Petra

Collective performativity in nursing home to hospital transitions

Frail elderly people, often living with a combination of clinical conditions, are anticipated to experience fluctuations over time, yet these can be interpreted as decline warranting medical investigation or intervention. For nursing home residents, this situation frequently results in multiple transitions in and out of hospital. Such transfers can result in frustration for all involved, may be arranged without expectation of improved quality of life for the resident, and are associated with a significant rate of in-hospital mortality. In this presentation, I will apply the theoretical lens of Butler's performativity to reflect upon discourses within my roles as an admitting hospital physician, and as a relative of a nursing home resident. I explore what may be at stake when staff practices are enacted within a normative framework that medicalises frailty. Tools such as protocols and checklists, intended to improve safety and quality of care, may contribute to constrained outcomes in staff communication and decision-making regarding nursing home to hospital transfer. I close by considering tensions for staff working within pre-existing procedural norms of risk-averse healthcare systems, which may override preferences of frail residents and their family, and where staff members' own agency may become diminished.

Llewelyn, Huw

Over-diagnosis from the perspective of a medical practitioner and teacher

When doctors, students, nurses and other health professionals are asked to verbalise their thought process when arriving at diagnoses and treatment decisions, they invariably use hypothetico-deductive reasoning [1]. It is the information used in the thought process that varies between these groups. The Oxford Handbook of Clinical Diagnosis [2] teaches this hypothetico-deductive reasoning process with over 500 pages of examples. It is based on a theorem derived from Bayes expanded rule (not the usual Bayes simple rule), which is described in detail in the final chapter

with its proof. The theorem identifies the principles and pitfalls of hypotheticodeductive reasoning when showing that rival diagnoses are improbable. Diagnoses are 'refuted' only if definitive criteria are present. It uses ratios of sensitivities and false negative rates (not false positive rates and likelihood ratios). The same reasoning process can be used to arrive at diagnostic and treatment criteria in a way that minimises over-diagnosis and over-treatment. This probabilistic mode of hypothetico-deductive reasoning is central to clinical practice and needs to be taken into account during research on assessing the usefulness of diagnostic tests. The way it is used to minimise over-diagnosis and over-treatment will be described in detail.

Saloni deSouza

Too Much of a Good Thing?

In the medical sphere, there is much discussion of where the fine line between 'too much' and 'too little medicine lies and how to tread it. This paper examines this issue from a philosophical perspective. My argument consists of three parts. Firstly, I establish criteria for what counts as 'too much medicine'. Secondly, I argue that even on a very narrow conception of what constitutes health -- the absence of disease -- there are some sufferers of chronic diseases (e.g. epilepsy, bipolar disorder), for whom illness is preferable to health, and others for whom apparent under or over--treatment is in fact preferable. The reasons for this are related to the nature of the disease, personal values and identity. I also address an anticipated objection from philosophers and medics to this picture: that such people are simply wrong. Finally, I turn to current medical practices, metrics and guidelines in treating these illnesses and suggest that there are three assumptions in play: health is the absence of disease, we should not look too closely at individuals, illness is bad for us. These, I suggest, are incompatible with the cases above and lead to too much medicine.

de Barra, Micheal

Reporting Bias Inflates the Reputation of Medical Treatments: A Comparison of Outcomes in Clinical Trials and Online Product Reviews

Why do people often hold unduly positive expectations about the outcomes of treatment? Perhaps people who have a positive outcome tend to tell more people about their disease/treatment than people with poor or average outcomes. Akin to the file drawer problem in science, this would systematically and positively distort the treatment's reputation. We might also expect such an over-reporting bias to inflate the average outcome in online medical product reviews. Method. Self-reported outcome data were extracted from user-generated reviews on Amazon.com and compared to RCT data for the same treatments using ANOVA. The sample included 1,675 reviews of cholesterol reduction (Benecol, CholestOff) and

weight loss (Orlistat) treatments. Results In three independent tests, average outcomes reported in the reviews were substantially more positive than the outcomes reported in the medical literature ($\eta 2 = .01$ to 0.06; p = .04 to .001). For example, average cholesterol change following use of Benecol is -14mg/dl in RCTs and -45mg/dl in online reviews. Discussion. People with good outcomes are more inclined to share information about their treatment; distorts the information available to others. People who rely on word-of-mouth reputation, electronic or real life, are likely to develop unduly positive expectations and engage in overuse.

Steele, Margaret

Having Obesity versus Being Fat: Philosophical problems with defining obesity as a disease.

In medical circles, there is still considerable debate over whether obesity is a disease. Outside the medical community, defining obesity as a disease is seen by many as a paradigmatic case of too much medicine. Fat acceptance advocates or advocates of Health at Every Size, for example, would argue that it needlessly pathologises fatness and thus stigmatises fat people. Those who see obesity as a matter of individual behaviour would say it allows overweight individuals to shirk their personal responsibilities. In both contexts, I argue that this debate suffers from too little medicine, in the sense that etiological and epidemiological questions about disease and obesity have been overshadowed by ethical, social and political concerns. I suggest that, in the case of obesity, one way to avoid too much medicine at the practical level is for medical researchers and philosophers (together with colleagues in other fields) to cooperate in disentangling, at the theoretical level, the ethical, social and cultural strands of the debate and to return to the questions 'What is a disease?' and 'Is obesity a disease?' I conclude by offering preliminary answers drawing on both philosophical definitions of disease and medical accounts of obesity.

Fuller, Jonathan

Simple Extrapolation and Overtreatment in Medicine

The most common approach to extrapolating from clinical trials according to a recent systematic review1 is as follows: extrapolate the relative effect size (e.g. relative risk) to the target population unless you have a compelling reason not to extrapolate. Philosophers call this approach 'simple induction' or 'simple extrapolation'. In this paper, I examine simple extrapolation using an interdisciplinary lens, drawing on empirical, medical methodology, and philosophical literatures. I argue that simple extrapolation's major flaw is that it is biased towards overextrapolation and overtreatment.

Three problems with simple extrapolation lead to overtreatment. First, it assumes that relative risks are generally generalizable, an assumption that lacks empirical and theoretical support. Second, it represents a weak argument from ignorance. Lastly, it's insensitive to the practical consequences of extrapolating. These problems suggest three principles for any solution to the problem of extrapolation in medicine or philosophy. First, the approach must be underwritten by theory that tells us when two populations are adequately comparable. Second, it must advise us how to use evidence to establish sufficient comparability. Finally, it must advise us when to accept generalizability for practical purposes and treat.

Livingstone-Banks, Jonathan

The Case for a Meta-Nosological Survey of Disease Classificational Practices in Modern Mainstream Medicine

There are a wide variety of ways by which diseases are classified and differentiated in modern medicine, including by symptom (syndromic), underlying cause (etiological), biological mechanism (pathogenetic), treatment, historical precedent, and through diagnostic exclusion. However, there is no universal classificatory schema that unifies how we map out the disease landscape. This project explores the options for a unified classificational schema, exploring the philosophical links with real-world problems, such as the problem of over-diagnosis. This sets the groundwork for future empirical work investigating the potential for real-world benefit in how we practice and research medicine.

There is a well-established tradition of changes in medical definitions on an individual scale, both by stipulation, and by evolution. Sometimes these changes have a strong realist assumption underlying them whereby the perceived benefit of the change is in getting closer to the truth of what the disease is like. In other cases it is more pragmatically based, whereby the perceived benefit is more in terms of our ability to treat the disease. By reimagining disease classification we may be able to render advantage to the treatment of diseases, improve our ability to research them, and impact on the ethical situations arising from healthcare.

Treadwell, Julian

Why General Practitioners care about "Too Much Medicine", and their role in addressing it.

In 2015 the Royal College of General Practitioners established a standing group on Overdiagnosis in response to movements around the world addressing the challenge of Too Much Medicine. This session will explore the drivers and themes which operate in primary care: expanding preventive medicine underpinned by widening disease definitions ; the imposition of activities by specialist enthusiasts ; political pseudo-solutions for difficult problems; audit and pay for performance, and the role of intellectual biases and instinctive beliefs. These will be illustrated with everyday clinical examples*, unpicking the evidence behind them to reveal the scale of overmedicalisation created in order that a few may benefit. We then see there are difficult choices to be made about what good healthcare looks like and what is possible with finite resources. This overview will open a discussion which will be relevant to all disciplines within healthcare sciences and all of us who are, or will be, patients.

Smart, Benjamin et al.

Do concepts of disease apply to "chronic kidney disease"?

Several philosophers of medicine have attempted to answer the question 'what is disease?' (Boorse 1977, 1978, 1997; Cooper 2002; Wakefield 1992; Smart 2016). Germund Hesslow (1993), however, has argued that although the concept of disease might be useful in some contexts, the notion is redundant when it comes to clinical decision making. Chronic kidney disease (CKD) encompasses a wide range of kidney health states from commonly prevalent sub-clinical, asymptomatic disease to rare end stage renal disease requiring transplant or dialysis to support life. Differences in severity are currently expressed using a 'stage' system similar to that used by oncologists, but unlike with cancer, early stage CKD in older patients is normal, of little concern, and does not require treatment. However, studies have shown (e.g. Horwood, SAPC 2015) that many patients find being informed of their "chronic kidney disease" distressing, even in its early stages. Using existing analyses of disease in the philosophy literature, we argue that the most prevalent stages of CKD are not, in fact, diseases. We conclude that, in many cases, diagnosing a patient with a disease is not only redundant, but a practice that should be avoided in order to maximise the wellbeing of patients.'

Iain Chalmers, Selena Ryan-Vig, Sarah Pannell, Astrid Austvoll-Dahlgren, and Andy Oxman Informed Health Choices Key Concepts and their application

The innovative Informed Health Choices (IHC) Project has developed educational resources to help people assess whether claims about the effects of treatments are likely to be trustworthy. The starting point for creating these resources was the identification of over 30 Key Concepts that people need to understand to become equipped to assess treatment claims. Two recently completed randomised trials have shown that IHC educational resources helped Ugandan primary school children and their parents to apply IHC Key Concepts in assessing treatment claims. Teaching and applying some IHC Key Concepts is relevant to addressing concerns

about 'Too Much Medicine'. Relevant Key Concepts include: 'Treatments can harm'; 'Association is not the same as causation'; 'Common practice is not always evidencebased'; 'More is not necessarily better'; and 'Earlier is not necessarily better'. These and other Key Concepts now provide an infrastructure for organising and presenting learning resources at <u>www.testingtreatments.org</u> and <u>www.students4bestevidence.net</u>. Several of the concepts have been shown to map onto the English School Science Curriculum.

A presentation of these applications of the IHC Key Concepts will be used to stimulate a discussion about whether adopting them can provide a useful framework for promoting critical assessment of claims about the effects of treatments.