Institution: The University of Oxford

Unit of Assessment: UOA32

Title of case study: Improving the Methodology, Ethics, and Implementation of Evidence-Based Medicine

1. Summary of the impact (indicative maximum 100 words)

Dr Jeremy Howick's research into philosophical issues concerning the nature of the evidence invoked in evidence-based medicine has led both to a revision of the standards for reporting trials, and to a redesign of the Oxford Centre for Evidence-Based Medicine 'Levels of Evidence': one of the most widely used systems for ranking medical evidence, and thereby for deciding whether treatments are effective, in the world. His research into philosophical issues concerning the ethics of using placebos in clinical trials and in clinical practice has influenced practitioners as well as patients by helping to determine how treatments are developed and applied. Through his research in both of these areas he has enhanced public understanding of the use of placebos.

2. Underpinning research (indicative maximum 500 words)

There are various philosophical issues that arise in connection with the evidence invoked in evidence-based medicine. Paramount among these are issues about the use of placebos. For instance, there are methodological issues concerning the level of evidence that the use of placebos affords; and there are ethical issues concerning the deception that their use involves. These issues are not only interesting in their own right: they are also interesting in their interconnection. Take the fact that placebo controls are often used in clinical trials when there is an established treatment with which the patients mistakenly think the new treatment is being compared: the deception involved here seems ethically problematic, as indeed does the fact that some of the patients are thereby being denied the benefits of the established therapy. But the justification that is normally given for the use of placebos in such cases is that placebo controlled trials give better evidence than trials using two active therapies. So the ethical issues about the use of placebos are directly connected to the methodological issues about the level of evidence that their use provides.

Dr Howick is a philosopher of science and ethicist who, since 2007, has held a non-clinical research fellowship in the Department of Primary Care Health Sciences at Oxford, where he leads a module on the history and philosophy of evidence-based healthcare. His research has been concerned with exploring the full range of these philosophical issues. He notes that there is no way of adequately addressing these questions without first grappling with some basic conceptual questions about what a placebo *is*. These questions are more difficult than they appear. For example, it is usually claimed that placebos are somehow inactive or have no specific effect, but one of the most interesting facts about them is precisely that they do often have a specific effect. Furthermore the term 'placebo' is used to describe a bewildering variety of treatments, ranging from sham surgery and sugar pills to attention controls. This wide usage exacerbates a problem that arises anyway, namely that a very good treatment may fail to outperform a placebo in a given trial simply because the placebo used in that trial is itself relatively effective, while a worse rival treatment may outperform the placebo that is used in another trial because the placebo used in that second trial is not at all effective. Another problem is that the term 'placebo' may be used whether or not the testing is double-blind, but whether or not the testing is double-blind may in turn have a significant subliminal bearing on how the patients react to the treatment that is administered to them.

In his article 'Questioning the Methodologic Superiority of "Placebo" Over "Active" Controlled Trials', Dr Howick exploits his answers to some of these basic conceptual questions to consider the reasons that are commonly given for thinking that placebo controlled trials afford better evidence than trials using two active therapies. He concludes that these reasons are inadequate, and that the ethical concerns about placebo controlled trials therefore remain unmitigated.

In the article 'What's in Placebos: Who Knows?' he and his co-authors (from the University of California at San Diego) note that there is no regulation concerning placebo composition – which is itself a further illustration of how widely the term 'placebo' can be used – and that, at the time, the great majority of trials involving pills or capsules (nearly 92%) and the majority of trials involving injections and other treatments (over 73%) fail to report the composition of the placebo concerned,

despite its obvious potential influence on the outcome of the trial. The authors conclude that this is another ethically and methodologically unsatisfactory feature of the common use of placebos.

In Dr Howick's book *The Philosophy of Evidence-Based Medicine* he turns his attention to the more overtly methodological issues about the nature and quality of the evidence invoked in evidence-based medicine and provides a theoretical framework for distinguishing between different levels of such evidence. And in 'The Evidence Underpinning Sports Performance Products', Dr Howick and others appeal to these revised levels of evidence to expose ways in which products that are supposed to improve sports performance are misleadingly advertised.

In 2012 a web-based questionnaire was used to survey UK General Practitioners (GPs) in an attempt to quantify the routine use of placebos in UK primary care. Dr Howick was the lead author of the 2013 report in which the results were published. It showed that placebos were one of the more commonly used treatments by GPs and raised unresolved ethical issues about how GPs approach informed consent, in relation to their prescriptions of placebos.

3. References to the research (indicative maximum of six references)

J. Howick (2009), 'Questioning Methodologic Superiority of "Placebo" Over "Active" Controlled Trials', in *American Journal of Bioethics* **9**. DOI:10.1080/15265160903090041.

This was published as a 'Target article' alongside 11 open peer commentaries, and Dr Howick's reply to these appeared in the same issue. According to the publisher the main article has been cited at least 17 times and the responding commentaries 13 times between them; according to Google Scholar the main article has been cited 27 times. In 2011, the American Journal of Bioethics had an impact factor of 4.083.

B. Golomb, L. Erickson, S. Sacks, S. Koperski, M. Enkin, and J. Howick (2010), 'What's in Placebos: Who Knows? Analysis of Randomized Controlled Trials', in *Annals of Internal Medicine* **153 (8)** 532-525. DOI: 10.7326/0003-4819-153-8-201010190-00010

According to Google Scholar, this article has been cited 23 times. In 2011, the Annals of Internal Medicine had an impact factor of 14.0 and acceptance rates for original research have been in the 6-8% range in recent years.

J. Howick (2011), *The Philosophy of Evidence-Based Medicine* (Oxford: Blackwell-Wiley). DOI: 10.1002/9781444342673

Review: "Jeremy Howick has written the most comprehensive and fair philosophical treatment of EBM to date" from A Broadbent (2013) Book Review in *Philosophy of Science* **80** pp. 165-168. The University of Chicago Press.

J. Howick et al (2012), 'The Evidence Underpinning Sports Performance Products: A Systematic Assessment', in *British Medical Journal Open* **2**. DOI:10.1136/bmjopen-2012-001702. Peer-reviewed.

Howick J et al. (2013) Placebo Use in the United Kingdom: Results from a National Survey of Primary Care Practitioners. PLoS ONE 8(3). DOI: 10.1371/journal.pone.0058247. Peer-reviewed.

4. Details of the impact (indicative maximum 750 words)

Dr Howick's work into philosophical issues concerning the ethics of using placebos in clinical trials and in clinical practice has helped to determine what types of trial are conducted and what types of treatment are used in clinical practice. It has also increased the understanding of the general public on the use of placebos.

(i) Impact on Clinical Tests and Clinical Practice

'Levels of evidence' had first been introduced in 1998 by the Oxford Centre for Evidence-Based Medicine, in an attempt to make both the process of finding appropriate evidence for diagnostic techniques, prognostic markers, therapeutic benefits, and economic analysis and the task of explicitly stating the results of that process feasible. On the strength of the research for his book *The Philosophy of Evidence-Based Medicine*, Dr Howick was commissioned by the Oxford Centre for Evidence-Based Medicine (OCEBM) to participate in the working group revising the 1998 levels. The updated version was published in 2011[(i)] and included not only new data but also the

new conceptual considerations that Dr Howick advances in his book. These new OCEBM levels of evidence constitute one of the most widely used systems for ranking evidence in the world: direct appeal is made to this system in deciding whether treatments are effective, whether diagnoses are accurate, how prevalent diseases are, how successful prognostic markers are, and ultimately which treatments shall receive approval for marketing. The system is thus used not only by medical researchers but also by care-givers, patients, and policy makers. Examples of the many and varied recommendations and clinical advice that incorporate this system are the *2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome* and clinical practice guidelines on sudden hearing loss that were published in *Otolaryngology* in 2012(ii). Discussions of the practising of evidence-based medicine, with links to the levels of evidence, are available on the Patient.co.uk website. The levels are also used in teaching, e.g. at the University of the Witwatersrand, South Africa(iii).

Following the ethical concerns expressed in the article 'Questioning the Methodologic Superiority of "Placebo" Over "Active" Controlled Trials' a change in clinical tests and clinical practice has been observed. Placebo use in clinical trials is controversial where an established treatment is available: clinicians are generally against its use while methodologists claim placebo use is sometimes required to establish efficacy. The article examined the controversy and specified well-defined criteria that need to be met in order for placebo controlled trials to be ethical. It is having an influence on the way policy makers think about placebo controls, as evidenced in the article 'The Rationale for Placebo-Controlled Trials: Methodology and Policy Considerations', by Franklin Miller, Senior Faculty of the National Institutes of Health and advisor to the United States Food and Drug Administration(iv). The research findings are also having a bearing on the way research on placebo controls is being conducted, both in the medical sphere(v) and in other areas such as social policy(vi). Specifically, the use of placebo controls, especially for complex interventions, is coming under increasing scrutiny.

In response to a draft of the survey results of placebo use by UK primary care practitioners the General Medical Council (GMC) issued a revision to their *Good Practice in Prescribing and Managing Medicines and Devices* guide in clarification of their stance on placebos(vii).

(ii) Impact on the Reporting of Trials

The article 'What's in Placebos: Who Knows?' prompted a clarification from the authors of the Consolidated Standards for Reporting Trials (CONSORT)(viii). CONSORT is a set of recommendations for the reporting of trials: it contains a checklist, and many of the top medical journals (including *British Medical Journal*, *The Lancet*, *Journal of the American Medical Association*, and *Annals of Internal Medicine*) require that potential authors complete the checklist before being considered for publication. Evidence for the impact that the article has had on how trials are reported is provided by the fact that, whereas at the time when the article was written, 83% of trials failed to report the composition of the placebo concerned, a later study by Ravikiran Sonawane and others, published in 2012(ix), showed that this figure, at least in respiratory medicine, had come down to 38%.

(iii) Increased Public Awareness

The findings of the article 'The Evidence Underpinning Sports Performance Products' formed the basis of an edition of BBC's *Panorama* in July 2012(x). Both article and documentary received widespread media coverage in the UK and internationally, e.g. in Canada, India, and Australia where additional comments were included from local sports experts and nutritionists(xi).The research and findings were also summarised on the NHS website in a discussion section on news headlines(xii) and have thereby contributed to changing the way in which people think about consuming sports drinks and spending money on expensive sports equipment.

The survey of placebo use by UK primary care practitioners was widely picked up by the media (including BBC and Channel 4 news, *The Times*, *The Independent*, and *The Daily Mail*)(xiii) and therefore increased public awareness of the issues. The article 'What's in Placebos: Who Knows?' also captured the attention of the general public: it was widely reported in the press (including Reuters(xiv), *The Wall Street Journal*, and *Science Daily*).

(iv) Advising Professional Groups

Following the well publicised findings of Dr Howick's research, he is often invited to talk to professional groups to discuss professional and methodological practices in a variety of fields. Recent examples include a Presidential Address to the American Neurophysiological Monitoring Society on 'Evidence-Based Neurophysiological Monitoring' in Salt Lake City, USA, in May 2012; a Plenary Lecture to the European Organization for Research and Treatment of Cancer on 'New Concepts in Levels of Evidence' in Brussels in December 2012, and a talk on 'The necessity of conducting randomized trials (but not placebo controlled randomized trials) for complex interventions in allied health professions' in London in May 2013. Following this last meeting Dr Howick was invited to author a follow up paper that will guide the use of placebos in UK physiotherapy trials[(1)].

5. Sources to corroborate the impact (indicative maximum of 10 references)

Testimony

[(1)]Email invitation to write follow up paper from Facilitator, AHPRN.

Other evidence sources

[(i)]OCEBM Levels of Evidence Working Group (Dr Howick and ten others), *The Oxford 2011 Levels of Evidence* (Oxford Centre for Evidence-Based Medicine)

[(ii)]Stachler RJ et al. 2012. Clinical practice guideline: sudden hearing loss. *Otolaryngology – Head Neck Surgery*. 2012 Mar;146(3 Suppl):S1-35. DOI: 10.1177/0194599812436449

[(iii)]http://libguides.wits.ac.za/content.php?pid=127828&sid=1932836

[(iv)]Miller, F. 2009. The rationale for placebo-controlled trials: Methodology and policy considerations. *American Journal of Bioethics–Neuroscience*, **9(9)**: 49–50. DOI: 10.1080/15265160903098408.

[(v)]Saunjoo LY et al. 2012. Clinical evaluation of liquid placebos for an herbal supplement, STW5, in healthy volunteers. *Complementary Therapies in Medicine*, **20(5)**: 267-274. DOI: 10.1016/j.ctim.2012.04.003

[(vi)]Morton, MH et al. 2012. Empowerment-based non-formal education for Arab youth: A pilot randomized trial, *Children and Youth Services Review*, **34(2)**: 417-425. DOI: 10.1016/j.childyouth.2011.11.013

[(vii)]GMC clarification on placebo use: http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp

[(viii)]Schulz, K et al. 2010. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials, *British Medical Journal* **210**: 340:c332. DOI: 10.1136/bmj.c332

[(ix)]Sonawane, R et al. 2012. 'Placebo Disclosure Rate in Randomized Controlled Trials Involving Critically Ill Patients', *American Journal of Respiratory and Critical Care Medicine* **186(5)** pp. 463-464. DOI: 10.1164/ajrccm.186.5.463a

[(x)]http://www.bbc.co.uk/programmes/b01l1yxk.

[(xi)]http://www.theaustralian.com.au/news/latest-news/sports-drinks-claims-debunked-report/story-fn3dxiwe-1226431088790

[(xii]http://www.nhs.uk/news/2012/07July/Pages/Gym-and-tonic.aspxNHS

[(xiii)]List of media articles ensuing from PLOS ONE survey article: http://www.plosone.org/annotation/listThread.action?root=63233

[(xiv)]http://www.reuters.com/article/2010/10/18/us-whats-placebo-idUSTRE69H51L20101018