Institution: University of Cambridge

Unit of Assessment: UoA 30 (Philosophy)

Title of case study: Medical Risk: Informing Public Policy on Hormonal Pregnancy Tests, Animal Welfare and Human Germline Manipulation

Period when the underpinning research was undertaken: 2007-2019

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Tim Lewens	Professor of Philosophy of Science	October 2002-present
Jesse Olszynko-Gryn	Wellcome Trust Postdoctoral Fellow	October 2013-December 2018

Period when the claimed impact occurred: 2015-2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Tim Lewens and Jesse Olszynko-Gryn's work on medical risk and its proper governance has had impact over three areas:

- Their work on the Hormonal Pregnancy Test (HPT) Primodos was partly responsible for the launch, and subsequent conduct, of an official inquiry into the regulatory handling of these tests.
- Lewens's work on the ethics of medical risk led to his being invited to join AstraZeneca's new AWERB (Animal Welfare Ethical Review Body). He has given training courses for AZ researchers, and has influenced the company's overall culture of care.
- Lewens's work with the Nuffield Council on Bioethics gave rise to decisive contributions to parliamentary debates on the legalisation of mitochondrial 'donation' technologies.

2. Underpinning research

The underpinning research on medical risk and its proper governance typifies the History and Philosophy of Science Department's priorities in the areas of history and philosophy of medicine, and its efforts to encourage interdisciplinarity for impact. The impact in question combines Olszynko-Gryn's archival historical research with Lewens's philosophical approach to risk, and draws on networks of scientists, sociologists and patient groups.

Olszynko-Gryn's research has focused on the history of pregnancy testing in Britain. This began with his (2014) PhD thesis, *Pregnancy Testing in Britain*, and has also included a series of essays focused on key episodes relating to the introduction and regulation of hormone pregnancy tests [R1]. His academic work on Primodos and other hormone pregnancy tests culminated in an article for which he was first author, which gives a detailed historical analysis of the development, adoption and withdrawal of these tests. These tests have been highly controversial because of strongly held views among patient groups that they caused significant harm to their unborn children [R2].

Lewens has had a longstanding interest in the ethics of risk, especially as it plays out in biomedical ethics [R3]. His work has addressed the proper understanding of the precautionary principle [R4], and the manner in which policy debates around risk need to be handled by both technical experts and those well-versed in ethical analysis [R5]. He has also

studied the ways in which different framings of risk-related information can reflect ethical judgements on the part of speakers [R5].His work has often focused on the case study of 'mitochondrial donation' technologies, and on other technologies that aim to influence germline inheritance [R5], [R6].He has argued for the need to take ethical values into account when deliberating over what appear to be purely technical questions about the regulation of scientific work. He has also used these insights as a basis for opposing strong divisions of advisory labour—for example between panels assigned to evaluate scientific questions on the one hand, and ethical questions on the other—when regulators consider how to manage the introduction of new technologies [R5].

3. References to the research

[R1] Olszynko-Gryn, J. (2013) 'When pregnancy tests were toads: The *Xenopus* test in the early NHS' *Wellcome History*, 51 pp. 1-3.

[R2] Olszynko-Gryn, J., E. Bjørvik, M. Weßel, S. Jülich and C. Jean (2018) 'A Historical Argument for Regulatory Failure in the Case of Primodos and other Hormone Pregnancy Tests' *Reproductive Biomedicine and Society Online* https://doi.org/10.1016/j.rbms.2018.09.003 34-44.

[R3] Lewens, T. (2007) 'Risk and Philosophy' in Lewens T. (ed.) *Risk: Philosophical Perspectives*. London: Routledge.

[R4] Lewens, T. (2010) 'The Risks of Progress: Precaution and the Case of Human Enhancement' *Journal of Risk Research* 13: 207-216.

[R5] Lewens, T. (2019) 'The Division of Advisory Labour: the Case of Mitochondrial "Donation"', *European Journal for Philosophy of Science* 9: 10. https://doi.org/10.1007/s13194-018-0235-3 .

[R6] Lewens, T. (2019) 'Blurring the Germline' *Bioethics* https://doi.org/10.1111/bioe.12606.

All outputs listed above have passed peer review within their respective journals, with the exception of [R3]. [R3] is a substantial discursive introduction to an edited collection from a major academic press. It was signed off by all contributors to the collection prior to publication, and has been cited over 10 times. The edited collection itself has been cited over 60 times (figures from Google Scholar). Therefore all underpinning work meets the 2* threshold.

4. Details of the impact

A. Primodos

Overview: Lewens's and Olszynko-Gryn's work on the Hormonal Pregnancy Test (HPT) Primodos contributed to the launch of an official review of the regulatory handling of these tests, and their work informed the deliberations of the official review panel. Key beneficiaries here include the review panel itself, members of the All Party Parliamentary Group (APPG) dedicated to HPTs, and members of the Association for Children Damaged by Hormone Pregnancy Tests.

The Primodos pregnancy test has been the subject of ongoing controversy on the grounds that it is regarded by some as the 'forgotten thalidomide'. For these reasons it has been the subject of repeated calls for official government inquiries. A report was finally completed on Hormone Pregnancy Tests in 2017 by the Medicines and Healthcare products Regulatory Agency's (MHRA's) Expert Working Group (EWG), partly on the basis of evidence submitted by Olszynko-Gryn [E1] [E2]. However the EWG's report was widely criticised for a range of inadequacies, including those highlighted by Olszynko-Gryn and Lewens.

Olszynko-Gryn organised an international conference in Cambridge (where Lewens spoke on Primodos and the precautionary principle) that brought together academic experts, practising lawyers, and patient groups, many of whom were critical of the EWG's approach [E3]. Lewens and Olszynko-Gryn also collaborated with the Sky News documentary film-maker Jason Farrell in the production of a film highlighting various shortcomings in the initial EWG report. The film was then screened in parliament—including a Q & A session for parliamentarians where Olszynko-Gryn was a participant—prior to the parliamentary debates discussing the need for further review. Olszynko-Gryn and Lewens contributed to meetings of the APPG on Hormone Pregnancy Tests, and they liaised closely with the campaigning group ACDHPT (Association for Children Damaged by Hormone Pregnancy Tests), to highlight a series of issues around the historical presentation of Primodos's use, and the framework for risk governance and risk communication. In these ways, their interventions were instrumental in building parliamentary support in favour of further inquiry into Primodos.

Partly thanks to these interventions, a new official review was launched in February 2018. This was the Independent Medicines and Medical Devices Safety Review (IMMDSR), led by Baroness Cumberlege, which reported on 8th July 2020. Yasmin Qureshi MP, Chair of the All-Party Parliamentary Group on Hormone Pregnancy Tests, confirms the role of Lewens and Olszynko-Gryn in the APPG, and in securing the new IMMDSR:

> 'The advice they gave … was instrumental in informing our MPs' successful calls in parliament for the launch of a new inquiry. [It] is not an exaggeration to say that Jesse and Tim's research played a key role in the launch of the…Cumberlege Inquiry…' [E4]

Both Olszynko-Gryn and Lewens went on to play roles in the new review. Olszynko-Gryn gave evidence at an oral hearing of the IMMDSR on 26th November 2018, and Lewens submitted written evidence to the inquiry [E5, E6]. He argued that, 'even when causal links [between Primodos and birth defects] are not established in a clear way—indeed, even when they are highly questionable—it can still be reasonable to take regulatory action in a precautionary manner. This is especially true when the value of a technology is in question, and when safe alternatives are available' [E6]. Lewens's basic argument was endorsed in the key finding of the Cumberlege report regarding Primodos: 'Given the concerns raised, the non-essential nature of HPTs and the provision of risk-free alternative tests, we consider that the CSD [Committee on Safety of Drugs] focus should not have been whether or not to issue a warning. **They should have recommended the withdrawal of the indication for use as a pregnancy test in 1967'** ([E7]; emphasis in original)**.**

Olszynko-Gryn and Lewens have also benefited the activities of the ACDHPT. Marie Lyon, the group's Chair, has written that 'The impact of the evidence provided by both Tim and Jesse undoubtedly played a huge part in the incredible and unexpected conclusions of the IMMDS report. This is the first time in more than 40 years that the failures of the Government Regulators in the 1960's &70s, have been identified and acknowledged in an Independent Government Review…ACDHPT owe a huge debt of gratitude for their continuing support.' [E8]

B. Astra Zeneca

Overview: Lewens's work on medical risk led to an invitation to join AstraZeneca's new AWERB (Animal Welfare Ethical Review Body). He has given training courses for AZ researchers, and has influenced the overall culture of care throughout the company. Key beneficiaries here include members of the AZ research community.

In 2017 Lewens was invited to join AZ's new Animal Welfare Ethical Review Board (AWERB) based on his track record of work on medical ethics and medical risk. Lewens has had a significant impact on the constitution and operation of the AWERB. In particular,

Lewens's longstanding research on the interpenetration of science and values has informed the committee's own approach to the tight links it draws between ethical approval and scientific validity. He has also given two bespoke training courses on medical ethics and medical risk for AWERB members. The acting Chair of the AZ AWERB comments thus:

> 'His impact on the AWERB group, has been considerable and has reached through into the AZ organisation in Cambridge. … His regular contributions to committee meetings have also resulted in an enlarged remit for the AWERB group. In particular, … he has helped us to articulate the importance of attending to the wellbeing of those who conduct research, in addition to the more usual focus on the animals. This has had concrete impact in terms of our renewed attention across the company to the 'culture of care' in place for our research staff.' [E9]

C. Inherited Genetic Disorders

Overview: Lewens's research on regulatory governance for risk has led to a role in the work of the International Commission on the Clinical Use of Human Germline Genome Editing; his earlier work with the Nuffield Council on Bioethics gave rise to decisive contributions to parliamentary debates on the legalisation of mitochondrial 'donation' technologies.

In February 2020, Lewens accepted an invitation from the International Commission on the Clinical Use of Human Germline Genome Editing to comment in detail on an early draft of their report on *Heritable Human Germline Engineering* [E10]. This joint report of the US National Academies and the UK Royal Society aims to provide a global translational framework for the potential use of germline genetic interventions. The report is expected to have considerable international regulatory influence, in part because its publication will be timed to feed into the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing.

Lewens's reputation in these matters derived from his earlier work with the Nuffield Council on Bioethics. The Nuffield Council Report on Mitochondrial DNA Disorders, co-authored by Lewens in 2012, expressed approval of two new experimental IVF techniques. Lewens was a member of the working party that authored this report, and he played a leading role in drafting the ethical framework within it. This involvement was confirmed by Council Director Hugh Whittall:

> '…[T]he role that Tim Lewens played in the preparation and drafting of this important report was particularly notable. His work in developing the ethical considerations, and especially in addressing issues around identity in relation to genetic therapies, formed a very substantial part of the arguments that sit at the heart of the report. His further contribution in applying these ethical discussions to the novel case of potential treatments for mitochondrial disorders was also critical to the success of this report.' [E11]

Lewens's work in authoring the Nuffield Council report pre-dates the REF review period; however, the impact of that work continued into the current period via the report's influence on parliamentary debate and subsequent new legislation (Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015). Following Parliamentary debates in both chambers, where parliamentarians repeatedly drew attention to the Council's positive ethical verdict with respect to mitochondrial donation [E12], both of the technologies endorsed by the report were approved in legislation passed in February 2015.

5. Sources to corroborate the impact

[E1] MHRA EWG Report cites Olszynko-Gryn's PhD thesis, pgs 6, 11, 105.

[E2] MHRA EWG Minutes – CONFIDENTIAL, pgs. 75, 78-9.

[E3] Cambridge conference on the Contested History of Hormone Pregnancy Tests, including presentations by Lewens and Olszynko-Gryn.

[E4] Testimonial from Chair of APPG on Hormone Pregnancy Tests.

[E5] Olszynko-Gryn's oral evidence to the IMMDSR.

[E6] Olszynko-Gryn and Lewens' written evidence to the IMMDSR, quotation on pg. 37.

[E7] Report of the Independent Medicines and Medical Devices Safety Review ('The Cumberlege Review'), quotation on pg. 73.

[E8] Testimonial from Chair of the ACDHPT.

[E9] Testimonial from Acting Chair of AZ AWERB.

[E10] Email of invitation from Associate Executive Director for Reports and Communication, US National Academies of Sciences, Engineering and Medicine.

[E11] Testimonial from Director of Nuffield Council on Bioethics.

[E12] Hansard references to citations of Nuffield Council Report in parliamentary debate, pgs. 2, 13, 19, 26, 60, 82, 88, 100, 118, 119, 131.