Institution: University College London

Unit of Assessment: 32 – Philosophy

Title of case study: Limits to individual choice in health research involving human subjects

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

Patients in clinical trials tend to have a very high drop-out rate which compromises results. Research by Sarah Edwards provided the key ethical framework for limiting individual choice in designing research involving human subjects. Edwards' research, showing how such designs can legitimately limit individual choices to withdraw, was incorporated into guidelines in the UK, Canada and the US, and by international bodies such as the World Health Organisation. In the UK, the research was also used to develop guidelines for ethics committees approving controlled trials.

2. Underpinning research (indicative maximum 500 words)

It was widely assumed that subjects of clinical trials reserve 'absolute (wholly inalienable) rights to withdraw from a programme of research at any time and without giving a reason. Herein, the right to withdraw is treated as a simple extension of the right to refuse to participate all together. Research by Dr Sarah J. L. Edwards (Senior Lecturer in Research Ethics and Governance at UCL, 2008–present) explores the moral justifications for limiting individual choice in order to improve methodological efficiency and promote autonomous participation (especially informed withdrawal) in different research designs and contexts. Edwards' work has included consideration of what consent means in research participation and of the adverse effects introduced by offering an unconditional 'right' of withdrawal. She used findings of this work to suggest that participants should, at consent, assume some responsibility for the internal validity of the trial.

There are two strands to this research. The first is a **philosophical analysis of justifications for placing limits on a research subject's right to withdraw** from research once initial consent has been granted. In 2011, Edwards developed the idea that research subjects should, at the time of consent, relinquish some of the (hitherto standard) unconditional rights to withdraw. She developed a philosophical and legal analysis of contractual relationships between researchers and their subjects, arguing that subjects cannot be said, individually and separately, to assume moral duties to future patients simply by consenting to participate in a trial. This is because any single subject cannot be said to have *caused* any individual patient harm in the future. Rather, a single subject contributes only to the statistical problem of missing data (resulting in underpowered or biased trial evidence), which could then mislead doctors resulting in the prescription of ineffective or harmful treatments [a]. This argument was based on earlier work (2005) in which Edwards developed the first philosophical analysis of autonomous participation in research (beyond the notion of simple consent) by limiting or qualifying rights to withdraw.

In April–June 2012, she completed a survey of 262 responding members of NHS research ethics committees, which found that they would welcome her proposal for policies specifically qualifying a research subject's right to withdraw in the context of weight management trials [b]. Methods of reducing withdrawal rates included provision of information at consent and at the point of withdrawal, in emphasising the probable consequences for the results, as well as asking those who withdraw for their reasons. These methods were piloted in trials conducted in July 2011–December 2012 through the UCL Clinical Trials Unit, including a Bupa funded surgical randomised control trial, QUEST (Quality of life after mastectomy and breast reconstruction) [c]. A focus group discussion in July 2013 with patients and the public showed similar support for the case to limit subjects' right to withdraw from trials.

The second strand is **a philosophical analysis of fair recruitment of people to cluster trials**, wherein consent from individuals to be randomly allocated, in groups or clusters, to treatments is limited to a greater or lesser extent**.** Cluster trials involve allocating groups (rather than individuals) to receive different treatments. In 2011, Edwards developed her preliminary taxonomy of consent by clarifying the options open to individual members of clusters and exploring the feasibility of individuals withdrawing from treatments assigned to these clusters. This, the first philosophical analysis of fair recruitment to cluster trials, explained their tendency, over traditional randomised controlled trials (RCTs), to exacerbate pre-existing inequalities between groups, showing why standard measures of redressing inequalities in research *ex post* may not be helpful [d]. How

clusters are identified and selected may be partially determined by their statistical efficiency (the fewer individuals within each cluster, the better). Edwards argues that this concern should be balanced against the perceived strength and social cohesion of pre-existing communities, and the consequences for overall health status. These questions can be gauged empirically through community engagement exercises. In Autumn 2012 Edwards and Dr David Osrin (UCL Institute for Global Health) organised the study of a target cluster trial, involving health resource centres in Mumbai, where groups were defined by geographical landmarks between dwellings for convenience. For this trial, the researchers enrolled 40 Mumbai slum communities of at least 24,000 households [e].

However, the problem of showing what needs to happen for the just treatment of patients in cluster trials, and what choices individuals should be allowed to make, might depend critically on the context within which the need for research arises. Edwards subsequently showed that, during a public health emergency involving a new pathogen, cluster trials could better respond to problems of justice than can traditional RCTs because cluster trials allow the introduction of new treatments incrementally (to groups which are already segregated to contain the communicable disease) thereby better respecting individuals' right to health [f].

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

[a] S. J. L. Edwards. Assessing the remedy: the case for contracts in clinical trials *The American Journal of Bioethics* 2011; 11(4): 1–10. doi: 10.1080/15265161.2011.560340. Funded by NIHR.

[b] C. Li, H. Davies, and S. J. L. Edwards. Ethics of patient retention in weight management trials: a survey in research ethics committee members*, Journal of Medical Ethics* (under review). https://www.ucl.ac.uk/cpjh/docs/ethics-patient-retention Funded by NIHR.

[c] N. Bidad, L. MacDonald, Z. E. Winters, S. J. L. Edwards, R. Horne. Views on the right to withdraw from randomised controlled trials assessing quality of life after mastectomy and breast reconstruction (QUEST): findings from the QUEST perspectives study (QPS). *Research Ethics* (under review). https://www.ucl.ac.uk/cpjh/docs/quest-right-to-withdraw Funded by Bupa.

[d] E. Conrad and S. J. L. Edwards. Inequalities and Fairness in Cluster Trials *Research Ethics* June 2011; 7: 58–65. doi: 10.1177/174701611100700205. Peer reviewed journal.

[e] S. Lignou, D. Osrin, G. Alcock, S. J. L. Edwards. Reconstructing communities in cluster trials? Project funded by MRC. Conference presentation, Hannover, Germany August 2013, funded by German Ministry of Education and Research. Available on request.

[f] S. J. L. Edwards. Drug discovery at the bedside: ethics of clinical science during a pandemic. *American Journal of Bioethics* 2013; 9; 3–14. doi: 10.1080/15265161.2013.813597. Funded by NIHR.

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S. J. L. Edwards (with Z. E. Winters and R. Horne). Bupa, QUEST Perspectives Study (QPS), £107,002, Jun 2011 – Dec 2012, supported the right to withdraw study.

S. J. L. Edwards (with J. Wolff). Walton Foundation, Political Advocacy and Cluster Trials. £15,000, Nov 2011 – Dec 2012, supported the study of cluster trials in Mumbai.

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

The potential social benefits of life and medical science are at once indeterminate and incalculable, and the research outlined above has helped to improve the validity and hence social value of controlled trials around the world. Beneficiaries include both the organisers of, and participants in, trials themselves, but also extend to all the patients to whom the results of those trials apply. Edwards' work relates to the considerable number of clinical trials run each year. For example, in 2012, the UK regulator approved 952 applications to run clinical trials of new medicinal drugs. In the same year, figures from the National Institute of Health Research (NIHR) show that almost 638,000 patients volunteered for clinical trials in the UK.

Those benefits accrue particularly from the use of Edwards' research to inform significant changes in the guidelines of bodies governing the conduct of research both internationally and in individual

countries (the UK, Europe, US, and Canada), including supporting improvements in the international governance of cluster trials delivered in developing countries. The numbers of such trials are increasing as more vaccines, educational and behavioural interventions are evaluated. In turn, this has led to changes in the ways in which research trials are conducted, particularly by ensuring the use of a more robust ethical framework for participants. Edwards' research has also benefited individuals participating in controlled trials by promoting autonomous participation (especially informed withdrawal) throughout trials – rather than only at the point of consent – and by protecting the rights and interests of individuals in defined communities recruited for cluster trials. In so doing, the research has helped to address the problem of 'missing data' from trial drop-outs.

In 2008 the Canadian National Institute for Health (NIH) funded a project [a] to produce the first internationally recognised guidelines on the ethics of cluster trials, based on Edwards' longstanding work on moral problems in such trials. Edwards was invited to join the project's Canadian Working Group, which met in Ottawa in 2009; this group comprised biostatisticians (including the person who invented the cluster design), methodologists, trialists, health policy professionals from WHO, and another bioethicist [1]. The Working Group wrote the **Ottawa Statement** on the ethical conduct of cluster trials, with a précis in the *BMJ* [1], which is used by researchers and ethics committees for guidance on the design and conduct of such trials. Edwards contributed particularly to Recommendation 14 of that Statement, which recognises that clusters may contain vulnerable participants and obliges researchers and ethics committees to consider the need for additional protections ensuring that consent procedures are appropriate for such participants. Furthermore, the Statement's fundamental recognition that inequalities may exist within clusters, and might be exacerbated by participation in the research, is explicitly based on [d] (see section 3 in [1]).

Following the Working Group meeting, its representatives presented the resultant Statement, including Recommendation 14, at a meeting in July 2013 of the US Secretary's Advisory Committee on Human Research Protections (SACHRP); this meeting prepared the first publicly available recommendations in the US on how the US Department of Health and Human Services (HHS) and Food and Drug Administration (FDA) regulations should be applied to cluster trials. These recommendations will, for the first time, guide investigators of **all FDA funded trials** of this sort as well as their Institutional Review Boards. The SACHRP discussed the recommendations at the meeting for final approval in October 2013 [2].

In 2010, Edwards contributed to a **World Health Organisation** (WHO) Working Party set up to produce guidelines on the ethics of patient safety research [3]. Those guidelines, which were published in 2013, provide guidance on patient safety in research taking place in resource-poor contexts. Recognising that many projects on patient safety resemble cluster study designs, Edwards' research [d] was cited to support the first guidance point that "vulnerable populations should not be differentially exposed to any extra risks brought up by the research without good reason, to avoid exacerbating inequalities". This point responded directly to the findings in [d].

As part of her research in Mumbai, Edwards piloted a study of this WHO guidance point in an international cluster trial of health services. The study was designed to develop and test a model strategy to improve women's and children's health in 40 Mumbai communities; it was funded by the Wellcome Trust and led by Dr David Osrin of UCL. The 24,000 households recruited, from February 2012 to present, benefited from access to health services [g].

In April 2013, the World Medical Association (WMA) released for public comment a draft revision of the **Declaration of Helsinki.** Although not binding in itself, it is widely recognised as the most authoritative guidance for human research ethics, and provides a basis for the regulation of research around the world. For example, it is enshrined in the EU Directive on, and UK regulations for, clinical trials which cover all investigational medicinal products. Following the release of the April 2013 draft revision, and based on her philosophical and empirical work, Edwards was invited in July 2013 by the Chair of the Working Party to draft a clause on the right to withdraw [4].

Edwards' research has further **improved the development and implementation of clinical trials through its use as the basis for professional training**. Again, the reach of these impacts extends both across and significantly beyond the UK. The **National Research Ethics Service** (NRES) oversees the operation of 69 NHS research ethics committees whose approval is legally required for clinical research projects in the UK. In 2008, Edwards was awarded a competitive

contract to provide research-based training to members of NHS and Social Care committees. Since 2008, she has provided training on consent and its limits for 160 committee members, based on her research and its uptake in professional and legal guidelines [5]. Ninety percent of members scored the content of her training as 4–6 on a six-point scale.

This training also led to sustained **refinements in the advice provided by the NRES**. In 2011 the NRES training lead, who had attended Edwards' training sessions, included her arguments in favour of limiting the right to withdraw from research (developed in [a]) in Article 6.2.2 of NRES' official policy document on Participant Information on "What will happen if I don't want to carry on with the study?" [6]. Governed by this document, **10,883 research projects** were approved by NHS and Social Care ethics committees in England between December 2011 and March 2013 [7]. The recognition of Edwards' framework as best practice is indicated by the fact that this Article will be retained in a major revision of this document in 2013 [6].

The **Association of Research Ethics Committees** (AREC), an independent umbrella group for research ethics committees, provides training and resources for more than 2,500 members across the UK. In 2012 it invited Edwards to draft a short guide to cluster trials after committee members asked for guidance on this topic, in light of the increasing numbers of cluster trials they were asked to review [9]. That draft was approved for publication in early 2013 by the AREC board and is now increasingly used for training, since AREC organises the full training programme for NRES [8].

Edwards drew on her research to develop and deliver a **large-scale continuous professional development programme** on research ethics and governance through UCL Partners, an academic health-science partnership based in the south-east of England. Between 2009 and July 2013, she trained 493 researchers over 7 one-day events, a substantial component of which focused on the issue of consent and its limits in research. The training course was rated 3–5 on a five-point scale by 92% of delegates [9].

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

[1] A copy of the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials. PLoS Med 9(11): doi: 10.1371/journal.pmed.1001346. Edwards' membership of the Working Group is confirmed in the Acknowledgements. For recommendation concerning fair selection of clusters included as a direct result of [d] see Recommendation 14 (citation 39).

[2] For the Ottawa Working Group / SACHRP preparation of recommendations for the application of US HHS and FDA regulations to cluster randomised trials: http://1.usa.gov/1fSqNI8 [PDF].

[3] For contribution to the International Expert Consultation on Ethical Issues for Patient Safety Research (May 2010) and incorporation of findings published in [d] into WHO's Ethical issues in patient safety research (2013): http://bit.ly/1aDNVml [PDF] pp. 4, 10, and 34 (footnote 10). An invitation to sit on WHO Working Group, Ethics of Patient Safety Research and confirmation that Articles were written as a direct result of [d] is also available on request.

[4] An email invitation from the Chair of the WMA Working Group on Declaration of Helsinki 2013 to draft an additional clause on limiting the right to withdraw is available on request.

[5] Copies of an email confirming Edwards' provision of training for NRES, and of participant feedback on that training, is available on request.

[6] Incorporation of findings in [a] in UK NRES Information Sheets and Consent Forms: Guidance for Researchers (2011): http://bit.ly/1eGx4Du [PDF] Article 6.2.2. Inclusion of right to withdraw similarly limited in the new version under consultation: http://bit.ly/1cLPxxc.

[7] For the number of research projects governed by this policy and by NHS and Social Care ethics committees see NRES Annual Reports: http://bit.ly/1b1zhsJ.

[8] For the UK AREC Short Guide on Cluster and stepped wedged cluster randomised trials: http://bit.ly/19rFIUA [PDF]. Email correspondence with the Vice Chair of AREC, confirming that the guide was drafted by Edwards based on [d], and is used in AREC training is available on request.

[9] Feedback forms from delegates who attended training in research ethics and governance provided through UCL are available on request.