

Study Results on the Bioethical Issues of Human Stem Cell Based Invention and Policy Recommendation

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1. Introduction

This research paper report's result of the empirical investigation conducted amongst thirty-one (31) expert respondents¹ from sixteen (16)² countries.³ Question nos. 1,⁴ 2,⁵ 3,⁶ 4,⁷

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¹ Profession of the Respondents are: Academic, Bioethicist, Lawyer, Patent Examiner, Patient Advocate, Physician, Researcher, Academic & Lawyer, Academic & Researcher, Academic, Bioethicist & Physician, Academic, Bioethicist & Lawyer, Academic, Lawyer & Patient, Bioethicist & Lawyer, Bioethicist & Researcher, Lawyer & Scientist, Patent Examiner & Researcher, Scientist & Researcher (any field). Arif Jamil, '*Patent Framework for the Human Stem Cells in Europe and the USA: Innovation, Ethics and Access to Therapy*' (PhD thesis, University of Bologna, 2016) 6, Table 1.2.

² Bangladesh, Botswana, Chile, Denmark, Egypt, India, Italy, Japan, Kyrgyzstan, Lithuania, Malaysia, Mexico, Spain, Suriname, UAE, and USA. *ibid* 5, Table 1.1.

³ This study result is part (unpublished) of the Ph.D. research project conducted by Arif Jamil from 2012 to 2016.

⁴ 'Do you bear any negative impression/ any prejudice about human stem cell research?

(a) Yes

(b) No'. Arif Jamil, '*Patent Framework for the Human Stem Cells in Europe and the USA: Innovation, Ethics and Access to Therapy*' (PhD thesis, University of Bologna, 2016) 176.

⁵ 'How do you perceive the terms "embryo", "human body" and "human life"?'

(a) They are same things and deserve the same rights.

(b) They are different forms of human being and deserve same rights.

(c) They are different entity, they have different status and they have different rights.' *ibid*.

⁶ 'How do you see the act of destruction of human embryo for the purpose of research and invention/ innovation?

(a) Unethical act, because it is against God's will (my religion does not allow it).

(b) Unethical act, because I consider embryo as human being or human body.

(c) Destruction for research and scientific experiments aimed at developing means to cure critical diseases can be allowed, despite the ethical issues divide opinions.

(d) Embryos are not human and if the destruction is a process that might bring medication for complicated and terminal diseases, I would not say that the act of destruction is unethical.

(e) Embryo at early stage is a different component from human being or human body. They are biological material of human origin and there is nothing unethical about its destruction.' *ibid* 177.

⁷ 'Do you have experience of dealing with a situation when conventional medication or treatment could not help?

(a) Yes, for myself

(b) Yes, not for myself but for family members

(c) Yes, for others

(d) No'. *ibid* 177.

5,⁸ 9⁹ and 11¹⁰ of the questionnaire comprised of thirteen (13) questions that are considered to have relevance to ethical issues in human stem cell research. The appendices are integral to verify the data analysis process and accordingly they were submitted for the review of the paper.¹¹

2. Methodology

Stata/SE version 13.1 is employed for the quantitative analysis in this study.¹² The introduction describes the data analysis' methodology, including the coding of the survey questionnaire variables, survey variable types and role-type classification and the statistical analysis method employed.

Each of the thirteen questions had several fixed answer options along with open option where the respondents expressed their views as a free response. As these options mainly comprised of texts and were categorical in nature, they were assigned a numerical value and this value was used to input the individual response chosen by each respondent. A cumulative survey table was then prepared using these values which consolidated all responses provided by the thirty-one (31) respondents.

⁸ 'Having a choice and at a critical stage of grave illness would you choose stem cell therapy for your family member, if it promises a cure (suppose already available as treatment)?

- (a) Yes, and it would be good if the State provides the expenses.
- (b) Yes, and willing to take it at personal expenses too, provided that I expect the costs of the treatment are reasonable.
- (c) Yes, and the insurance should cover it.
- (d) Yes (*If you want to mention a reason or circumstances other than mentioned already, you may write here*).....
- (e) No. (*If you want to mention a reason, you may write here*).....'. *ibid.*

⁹ 'Which application of human embryo can be permitted according to your opinion?

- (a) Commercial and industrial application for therapeutic purposes
- (b) For research purposes
- (c) For both the above
- (d) None of the above'. *ibid* 178.

¹⁰ 'Do you consider that the benefits of hESC (human Embryonic Stem Cell) research is more important than the risks and costs associated to it?

- (a) Yes
- (b) No'. *ibid.*, 178.

¹¹ Appendix A: Questionnaire, Appendix B: Legend and Codes, Appendix C: Cumulative Survey Table, Appendix D: Predictor-Response Table, Appendix E: Stata/SE Code Translation, Appendix F: Stata/SE 13.1 Logistic Regression Output, Appendix G: Logistic Regression Total Output: Stata/SE 13.1, Appendix H: Logistic Regression Output Stata/SE 13.1: Results showing Significance and Results showing Promising Association/Trend.

¹² Stata (stands for Statistical Data) is an integrated statistical software package. This is a general purpose software with data analysis, data management and graphics capabilities.

Most of the suggested options in the questionnaire are categorical while a few variables like age group, GNI (Gross National Income), etc. are quantitative in nature. However, assigning number values to each variable responses (whether categorical or quantitative) make them all amenable to further statistical analysis.¹³ The next step was to look for possible association between different variables and how they differed among different respondents. Accordingly, a variable role-type classification table was prepared where some variables were hypothesized to be ‘predictor variables’ (synonymous to ‘independent’ or ‘explanatory’ variables).

Predictor variables dictate the outcome of other variable known as the ‘response variable’ (synonymous to ‘dependent variable’). Predictor-response associations were compiled into a predictor-response table and tested with statistical analysis software. The *complete table* can be found in appendix D.

Possible association between the predictor and the response variables are analyzed with statistical and data analysis tools, Stata/SE version 13.1. Several different tests have been applied but the logistic regression analysis, among the tests tried, seemed to be the best fit for a survey performed by ‘convenience sampling’ and having a size of thirty-one (31) responses. To carry out binary logistic regression analysis, it was necessary to further split down the variables with multiple options into logical binary categories (where the response was either ‘yes’/1 or ‘no’/0).

The recoding of variables into binary variables and their interpretation is explained in appendix E. These codes are eventually used in the programming language of Stata/SE 13.1 to run logistic regression analysis. A complete set of the test output screenshots of all the associations tested in Stata/SE 13.1 can be found in appendix F. Three different tables were subsequently prepared where the results of the logistic regression are shown in terms of odds ratio (OR) and two-tailed 95% confidence interval (CI) with each OR assuming an alpha level of 0.05 (Appendices G and H). The statistically significant results and those showing promising association/trend were interpreted (Appendix H).

Arif Jamil and Tania Sultana Bonny reported about this study previously that ‘[t]he sample size despite being relatively small is acceptable from the statistical point of view.’¹⁴

¹³ Every statistical test has limitation. The statistical analysis methodology here was opted based on the *study design* and the available *sample size*.

¹⁴ Arif Jamil and Tania Sultana Bonny, ‘Fostering Innovation and Affordability: An Empirical Study Delving into Intellectual Property Protection of Human Stem Cell Based Invention/Innovation’ (2014) 3(2) NTUT Journal of Intellectual Property Law & Management 133, 136--37.

3. Survey Results of the Empirical Study Conducted Among the Experts

This part of the paper provides the results of the empirical investigation. Variables derived from the questionnaire included demographic features of the respondents and individual questions. Some of them were hypothesized to be *independent* or *predictor* while others were *dependent* or *response* variables. Univariate logistic regression analyses revealed associations having statistical significance (at an alpha level of 0.05) or showing positive trends and involved the following *predictor* variables:

- Demographic features, e.g. profession, age group, country economy (GNI);
- Perception about ‘embryo’, ‘human body’ & ‘human life’; embryo destruction and any negative impression/prejudice about human stem cell research (Q1 - Q3);
- Experience of dealing with a situation of conventional medication failure and willingness to choose stem cell therapy at critical stage of grave illness (Q4 - Q5);
- Perceived benefits of hESC research as compared to the risks and costs associated to it (Q11).

Following are the summarized results of logistic regression analysis.

3.1. Predictor: Demographic Features

Among the various demographic features, *profession* turned out to be an important predictor or independent variable. Compared to the other professionals, respondents belonging to the *academia* conveyed the following responses:

- 12.9 times more likely to *discourage any application of human embryo* ($p=0.031$; OR= 12.85713; 95% CI OR = 1.266369 - 130.5353);
- 91.25% *less likely* to consider that the *benefits of hESC research is more than the risk and costs* associated to it ($p=0.04$; OR= 0.0875; 95% CI OR = 0.008569 - 0.8934874).

Therefore, majority (92.22%) of the respondents in the *academia* did not support the *application of human embryo* for commercial and industrial (therapeutic), research or *both purposes* ($p=0.031$; OR= 0.0777779; 95% CI OR = 0.0076608 - 0.7896593).

Logistic regression analysis with some other professions as predictors also showed *positive trends* although they were *not significant* at an alpha level of 0.05. For instance, compared to the other professionals:

- Respondents who are *patent examiners* were 9.2 times *more likely* to consider that *embryos, human body and human life* have the *same rights* ($p=0.093$; OR= 9.199997; 95% CI OR = 0.6915986 - 122.383);

- Respondents serving as *patent examiners and researchers* were both against *any type of application of human embryo* ($p=0.063$, $OR=12$, $95\% CI OR = 0.870605 - 165.4022$; $p=0.061$, $OR=6.333333$; $95\% CI OR = 0.9196008 - 43.61796$ respectively), be it commercial and industrial (therapeutic), research or both ($p=0.063$; $OR=0.0833333$; $95\% CI OR = 0.0060459 - 1.148627$; $OR=0.1578947$ & $p=0.061$; $95\% CI OR = 0.0229263 - 1.087428$ respectively).

3.2. Predictor: Perception About Embryo, its Destruction and Any Negative Impression/Prejudice About Human Stem Cell Research (Q1-Q3)

Statistically significant association was observed when perception of ‘Embryo’, ‘Human body’ and ‘Human life’ was considered as a predictor. For instance, *respondents who perceived that*

‘Embryo’, ‘Human body’ and ‘Human life’ have the same rights also:

- Considered human *embryo destruction as unethical* ($p=0.001$; $OR=132$; $95\% CI OR = 7.15426 - 2435.472$);
- Was against *any application of human embryo* ($p=0.011$; $OR=14.66667$; $95\% CI OR = 1.828004 - 117.6754$).

More precisely, *opposed the application of human embryo* for commercial and industrial (therapeutic), research or *both purposes* ($p=0.011$; $OR=0.0681818$; $95\% CI OR = 0.008498 - 0.5470447$).

On the other hand, *respondents who perceived that ‘Embryos’, ‘Human body’ and ‘Human life’ are different entities and have different rights* also:

- Considered the *benefits of hESC research more important* than the risks and costs associated to it ($p=0.049$, $OR=7.2$; $95\% CI OR = 1.008718 - 51.39196$);
- Was against any application of human embryo ($p=0.02$; $OR=0.0631579$; $95\% CI OR = 0.0061144 - 0.6523801$).

More precisely, *opposed application of human embryo* for commercial and industrial (therapeutic), research or *both purposes* ($p=0.02$; $OR=15.83333$; $95\% CI OR = 1.532849 - 163.5481$).

Any *negative impression/prejudice* about stem cell research was found to be another *significant* predictor. Contrary to others, *respondents who had any negative impression/prejudice* about stem cell research were also:

- More likely to *oppose* any application of human embryo ($p=0.043$, $OR=16$; $95\% CI OR = 1.092859 - 234.2479$);
- Consequently were *94% less likely* to support application of human embryo for commercial and industrial (therapeutic), research or *both purposes* ($p=0.043$; $OR=0.0625$; $95\% CI OR = 0.004269 - 0.9150308$).

Perception on *embryo destruction* when used as a predictor also showed some statistically significant associations. For example, as compared to others, *respondents who deemed embryo destruction as unethical*:

- Did not support permitting any application of human embryo ($p= 0.008$; OR = 29.33333; 95% CI OR=2.404497 - 357.8481);
- Specifically opposed the application of human embryo for commercial and industrial (therapeutic), research or both purposes ($p= 0.008$; OR = 0.0340909; 95% CI OR=0.0027945 - 0.4158875);
- Did not consider that the benefits of hESC research are more important than the risks and costs associated to it ($p= 0.01$; OR = 0.0375; 95% CI OR=0.0030632 - 0.4590746).

Some other associations related to respondent's *impression and prejudice* to stem cell research and their *prior experience of dealing with conventional medication failure* showed *promising association/trend* although these associations were *not significant* at an alpha level of 0.05. For instance, respondents:

- With *no negative impression/prejudice* about stem cell research were also 11 times ($p= 0.074$; OR= 11; 95% CI OR = 0.7958456 - 152.0395) *more likely not to consider human embryo destruction as unethical* compared to those having any such impression/prejudice;
- Having *prior experience of conventional medication failure* were *more likely to perceive* that 'Embryos', 'Human body' and 'Human life' are *different entities and have different rights* compared to those who had no such experience ($p= 0.077$; OR= 4.083333; 95% CI OR = 0.860764- 19.37071) and thus were *less likely to consider* these entities having the *same rights* ($p= 0.088$; OR= 0.2; 95% CI OR = 0.03156 - 1.267428). The odds of these respondents opting for application of human embryo for *research purposes only* were also *less* ($p= 0.088$; OR = 0.2; 95% CI OR= 0.03156 - 1.267428).

3.3. Predictor: Perceived Benefits of hESC Research as Compared to the Risks and Costs Associated to it (Q11)

Univariate logistic regression analysis also revealed that the *perception* of the respondents on the relative *benefits of hESC research* as compared to the *associated risks and costs* was a significant predictor of *how they deemed application* of human embryo. A statistically significant number of respondents who believed that the *benefits* of hESC research are *more important* than the inherent *risks and associated cost* also:

- Supported that *application of human embryo should be permitted* for commercial and industrial (therapeutic), research or both purposes ($p= 0.002$; OR = 110; 95% CI OR= 5.832849 - 2074.458).

Therefore, were very *less likely* to oppose any application of human embryo ($p=0.002$; OR =0.0090909; 95% CI OR= 0.0004821 - 0.1714428).

The following figure summarizes the variables of question nos. 1, 2, 3, 4, 5, 9 and 11 within the questionnaire that resulted in *significant* association in regression analysis or showed *promising trends*.

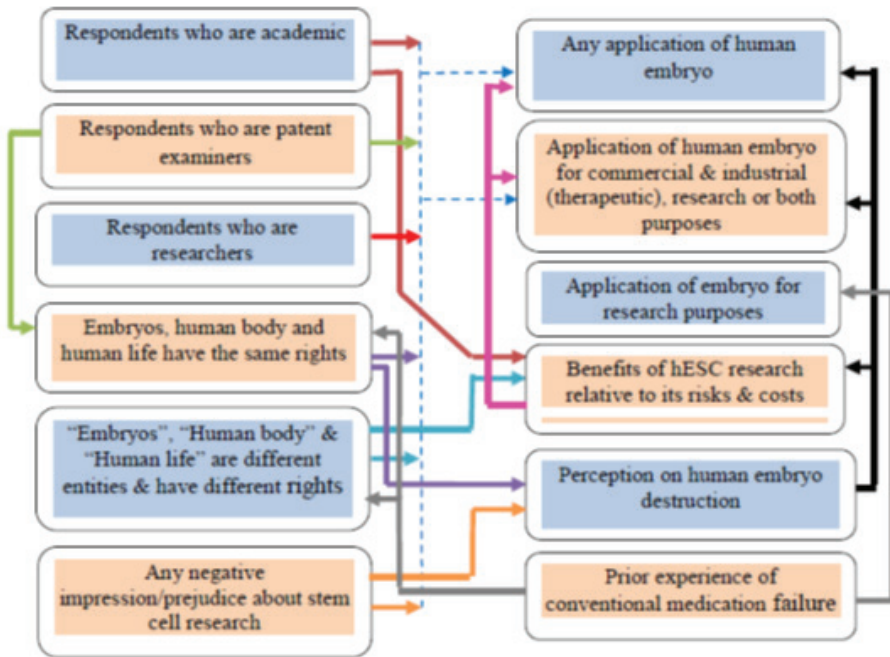


Figure 1: Logistic regression analysis summary (significant & promising association/trend results) of question nos. 1, 2, 3, 4, 5, 9 and 11. The common blue dotted line is connected with six predictors on the left. To avoid using too many arrows for the same response on the right, all the predictors showing similar response are connected with the blue dotted line and then that line (blue dotted) joins the variables (two) on the right).

4. Summing Up

The findings from the data analysis can be summed up as following:

Firstly, there are opposition from certain quarters (e.g., academia)¹⁵ against the use of human embryo in stem cell research and invention. Respondents, who perceived that ‘embryo’, ‘human body’ and ‘human life’ have the *same rights*, *opposed* the application of human embryo for commercial and industrial (therapeutic) research or both purposes.¹⁶

¹⁵ $p=0.031$; OR= 0.0777779; 95% CI OR = 0.0076608 - 0.7896593.

¹⁶ $p=0.011$; OR= 0.0681818; 95% CI OR = 0.008498 - 0.5470447.

On the other hand, respondents who perceived that ‘embryos’, ‘human body’ and ‘human life’ *are different entities and have different rights* also *opposed* the application of human embryo for commercial and industrial (therapeutic), research or both purposes.¹⁷ However, this group considered the benefits of hESC¹⁸ research more important than the risks and costs associated to it.¹⁹

Respondents who deemed embryo destruction as unethical opposed the application of human embryo for commercial and industrial (therapeutic), research or both purposes²⁰ and did not consider that the benefits of hESC research are more important than the risks and costs associated to it.²¹

Secondly, noticeable discovery of the survey are the following *promising association/trend*, though not significant at an alpha level of 0.05:

- respondents having ‘experience of conventional medication failure’ were *more likely to perceive* that ‘embryos’, ‘human body’ and ‘human life’ are *different entities and have different rights* compared to those who had no such experience²² and so were *less likely to consider* these entities (‘embryos’, ‘human body’ and ‘human life’) having the *same rights*.²³ This findings show that personal experience plays an important role in ‘how we see things’.
- Respondents with NO negative impression/prejudice about stem cell research were also 11 times²⁴ more likely NOT to consider human embryo destruction as unethical compared to those having any such impression/prejudice.

Thirdly, the study revealed that the ‘perception’ of the respondents plays an important role. A statistically significant number of respondents who believed that the *benefits* of hESC research are *more important* than the inherent risks and associated cost also supported that application of human embryo should be permitted for commercial and industrial (therapeutic), research or both purposes.²⁵ Therefore, were very less likely to oppose any application of human embryo.²⁶

¹⁷ p= 0.02; OR= 15.83333; 95% CI OR = 1.532849 - 163.5481.

¹⁸ Human Embryonic Stem Cell.

¹⁹ p= 0.049, OR= 7.2; 95% CI OR = 1.008718 - 51.39196.

²⁰ p= 0.008; OR = 0.0340909; 95% CI OR=0.0027945 - 0.4158875.

²¹ p= 0.01; OR = 0.0375; 95% CI OR=0.0030632 - 0.4590746.

²² p= 0.077; OR= 4.083333; 95% CI OR = 0.860764- 19.37071.

²³ p= 0.088; OR= 0.2; 95% CI OR = 0.03156 - 1.267428.

²⁴ p= 0.074; OR= 11; 95% CI OR = 0.7958456 - 152.0395.

²⁵ p= 0.002; OR = 110; 95% CI OR= 5.832849 - 2074.458.

²⁶ p= 0.002; OR =0.0090909; 95% CI OR= 0.0004821 - 0.1714428.

5. Conclusion by Way of Recommendation

Based on the findings in first part of section 4, it is recommended that use of human embryo in the stem cell research and invention is carefully and strictly regulated. Apart from respecting the Oviedo Convention on Human Rights and Biomedicine, 1997²⁷, every country should have clear bio policy and law (Life Sciences' Regulation) in this regard. The State has to answer and know for itself before making law on this subject:

- i. which experiments (derivation technique) on the embryo for the stem cell derivation should be allowed;
- ii. to what extent (commercial/industrial purposes for therapeutic reasons and/or research purposes) human embryo can be allowed to be used; and
- iii. embryos collected from which source (donated/purchased/IVF (in-vitro fertilization) redundant) can be allowed for the stem cell research.

After answering these questions, a country has to find out what kind of law and policy conform to its ethical standard and meets the scientific ambitions. If the country does not want to be the 'market only' for healthcare goods, it will have to promote research and development. The author believes from the experience that embryonic stem cells remain an important kind for the human stem cell research and stem cell-based inventions.

If the biolaw (law in life sciences) of a country is too conservative and too strict about embryonic stem cell research, it may isolate itself from the global trend in regenerative medicine. The pioneering research on human stem cells (regenerative medicine) are conducted in hi-tech and liberal but properly regulated countries like Japan, UK and the USA.²⁸

Second and last part of findings in section 4 revealed certain intriguing findings and they propel to underscore the need of science education. It also hints that diversity of experience and personal background is an important factor influencing the choice to embrace scientific developments. Legislators need to be educated and the law needs to be 'progressive and able' to guide the society to adapt with the invention.

Legal definitions of scientific terminologies have to be proper and accurate (from the scientific point of view), objective (from the scientific, ethical and philosophical point of view) and well-explanatory (meaning a simple reading explains it all).

²⁷ Council of Europe, 'Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine' <<https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/164>> accessed 7 July 2018.

²⁸ Arif Jamil, '*Patent Framework for the Human Stem Cells in Europe and the USA: Innovation, Ethics and Access to Therapy*' (PhD thesis, University of Bologna, 2016) 23-52.

Appendices²⁹

Appendix A: Questionnaire

Appendix B: Legend and Codes

Appendix C: Cumulative Survey Table

Appendix D: Predictor-Response Table

Appendix E: Stata/SE Code Translation

Appendix F: Stata/SE 13 Logistic Regression Output

Appendix G: Logistic Regression Total Output: Stata/SE 13

Appendix H: Logistic Regression Output Stata/SE 13.1: Results showing Significance and Results showing Promising Association/Trend

²⁹ Soft/Print-copy of the appendices was supplied for the review. For brevity reasons, contents of these appendices are not published with this article.