PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Consent for the use of human biological samples for biomedical research – a mixed methods study exploring the UK public's preferences
AUTHORS	Lewis, Celine; Clotworthy, Margaret; Hilton, Shona; Magee, Caroline; Robertson, Mark; Stubbins, Lesley; Corfield, Jule

VERSION 1 - REVIEW

REVIEWER	Wendy Lipworth Postdoctoral Research Fellow Australian Institute of Health Innovation, University of New South Wales Australia I have no competing interests.
REVIEW RETURNED	19-Apr-2013

THE STUDY	I am not statistically trained so cannot comment on the appropriateness of the statistical methods used.
GENERAL COMMENTS	I think some more needs to be said about the fact that focus group participants were not given the option of specific consent to every project. Does this affect the results? If not, why not?

REVIEWER	David M Shaw, Institute for Biomedical Ethics, University of Basel, Switzerland. No competing interests. Bernice S Elger, Institute for Biomedical Ethics, University of Basel, Switzerland. Cemter for Legal Medicine, University of Geneva, Switzerland. No competing interests.
REVIEW RETURNED	06-May-2013

THE STUDY	One limitation that is not mentioned is that participants were not asked about whether they would prefer "stronger" consent models for entities that they trust less, eg. industry. No power calculation is provided for the survey.
RESULTS & CONCLUSIONS	Some of the data is not reported in the paper
REPORTING & ETHICS	The responses concerning participants' attitudes regarding different entities are not reported in the paper (questions 7 and 8 in the focus groups, and q.22 in the survey). The survey results for q.22 are available in the appendix, but there is no trace of the focus group responses. This is unusual, particularly given the industry funding of the paper, and the fact that the omitted results are unfavourable to industry. These results should be reported and discussed in the paper.

	Participants were not informed about industry involvement in the study; the PIS states only that the University of Manchester and Genetic Alliance UK (a charity) were involved. This could amount to an undeclared conflict of interest.
GENERAL COMMENTS	This is an important study on the attitudes of the UK public to biobank donation and consent. On the whole, it is well-conducted. However, there are a couple of issues relating to the study's industry funding and reporting of its industry-related results. First, the PIS did not mention industry involvement in the study, which it clearly should have done. Second, both the focus groups and the survey included questions regarding participants' view on different entities handling donation. The results of these questions are not reported in the paper, which is rather suspect given that Appendix V indicates that people trusted industry less than other entities. It appears that industry involvement was hidden in recruitment to the study and that results unfavourable to industry have been omitted, which is unfortunate. These results should be reported and discussed, and another limitation of the study mentioned: it did not examine how people's views on consent and data linkage might vary according to which entities the data is to be shared with. Other comments: 1. It should be stated how many participants were in each focus group. 2. Why were there no participants from Wales or NI for the focus groups? 3. It is not stated whether survey respondents were paid; the assumption is that they were as they are "recruits" of a survey company. This should be clarified. The size of the honorarium for focus group members should also be stated. (It is possible that focus group members gave more "cooperative" responses than survey participants because they were paid (or paid more).) 4. A power calculation should be provided for the survey sample size. 5. The results section should also provide data on the survey results for the importance of consent and focus group results on preferred methods; at present only survey results on methods and group results on importance are included. 6. The definition of an ethics committee is slightly misleading as they normally only have lay representatives as members, not patients. 7. It is interesting that participants favoured an "active choice" over a "passive choice", but it is not clear exactly what they meant. This should be discussed further, as it could be argued that all choices are active regardless of how they are communicated. 8. Similarly, it is interesting that participants said that "opt-in" is truly informed consent. The information provided to potential donors is what guarantees that consent is informed; this is a different issue from the actual consent mechanism. While participants might not have realised this, it should at least be mentioned in the discussion.

REVIEWER	Karoliina Snell, DSocSc, Post doctoral researcher Biomedicine in Society (BitS) Research Platform Department of Social Research University of Helsinki

	Finland No competing interests
REVIEW RETURNED	07-May-2013

THE STUDY	For methods of analysis: There are many terms (broad, narrow, blanket, dynamic...) for different types of consent. I would like to have a short explanation: why these particular terms (generic, tiered, specific) and the respective definitions were chosen? Where are they derived from - i.e. UK practice, some report?
RESULTS & CONCLUSIONS	Results are discussed in light of previous evidence, but the literature could be broadened. There are for example European comparisons (i.e. Eurobarometer 341) that would contextualize attitudes in UK to European trends. And also numerous other national case studies i.e. Valle-Mansilla (2010) Spain; Ursin et al. (2008) Norway, Sweden, Denmark; Ducournau & Strand (2009) France - that either make a good comparison or provide information about the meaning of informed consent to people. This latter point could be developed a bit further in the article. Was there a difference between patients and "non-patients"? This was not reported in the article? In our study, we found interesting differences and similarities between patients and citizens. Tupasela & Snell: "National interests and international collaboration" in New Genetics and Society interesting as it is also a mixed methodology study (survey, focus groups & interviews).

VERSION 1 – AUTHOR RESPONSE

Reviewer: Wendy Lipworth
Postdoctoral Research Fellow
Australian Institute of Health Innovation, University of New South Wales Australia

I have no competing interests.

I am not statistically trained so cannot comment on the appropriateness of the statistical methods used.

I think some more needs to be said about the fact that focus group participants were not given the option of specific consent to every project.
Does this affect the results? If not, why not?

The reason we decided to add this second specific consent option in the survey was first because of the concern focus group participants had about samples being wasted, and second because of the possibilities (with new online technologies) for dynamic consent whereby donors may be able to track and consent their sample for each project it might be used for. It was for these reasons that we decided to add it as an option in the survey. Given that the key reasons focus group participants preferred generic consent were that it gave most flexibility to researchers, was more straightforward and was simpler to understand; it is unlikely that the option of specific consent for every new study would have been preferable for those whose preference was generic consent. Nevertheless, we agree this is an important point that should be addressed and have therefore added the following sentence in the limitations:

Focus groups participants were not presented with the option of ‘specific consent – for every new

study' (they were only given 'specific consent – once only'). This may have been an attractive option for some given that a concern raised was biosamples being wasted. However, given that the key reasons participants' valued generic consent were because it provided most flexibility to researchers and was most straightforward to administer, this seems unlikely.

Reviewer: David M Shaw, Institute for Biomedical Ethics, University of Basel, Switzerland. No competing interests.
Bernice S Elger, Institute for Biomedical Ethics, University of Basel, Switzerland. Cemter for Legal Medicine, University of Geneva, Switzerland.
No competing interests.

One limitation that is not mentioned is that participants were not asked about whether they would prefer "stronger" consent models for entities that they trust less, eg. industry.

Whilst trust in industry did appear to be a concern for some people during focus group discussion, this specific issue (preference for stronger consent models for such entities) was not raised. However, we agree it would have been interesting to explore this issue. We have raised this as a point in the limitations:

In addition, given time and resource constraints we were unable to explore whether 'stronger' consent models would have been preferable for organisations that donors trusted less. This is an area that would be worth exploring further in future research.

No power calculation is provided for the survey.

We have added the following information in the Methods section (under Survey) to address this point:

The sample size required depends on the number of predictors, the expected effect size and the level of power. According to Miles and Shevlin [Miles, J. N. and Shevlin, M. (2001) Applying regression and correlation: a guide for students and researchers. London: Sage.], if we are expecting a small effect size, a sample size of 600 is considered adequate to achieve a high level of power 0f 0.8 (a benchmark suggested by Cohen [Cohen, J. (1988) Statistical power analysis for the behavioural sciences (2nd ed.). New York: Academic Press.]) for four predictors. As highlighted in Table 2 we can formulate at least four hypothesis, for example, people from a higher socio-economic group are more likely to donate biosamples than those from lower socio-economic group. With a sample size of 1000, this study would provide highly reliable results.

The responses concerning participants' attitudes regarding different entities are not reported in the paper (questions 7 and 8 in the focus groups, and q.22 in the survey). The survey results for q.22 are available in the appendix, but there is no trace of the focus group responses. This is unusual, particularly given the industry funding of the paper, and the fact that the omitted results are unfavourable to industry. These results should be reported and discussed in the paper.

Due to the large number of questions addressed in the study it would not have been possible to present the results for all the questions in one paper, hence we divided the results into two separate papers; one focusing on consent models and one on uses of samples. This was discussed in the Introduction where we say "Public willingness to donate biosamples, views on donation of different biosample types, and conditions of their use are reported elsewhere (Public views on the donation and use of human biological samples in biomedical research – a mixed methods study, 2013, unpublished manuscript)."

We have however made it clearer that the second paper will focus on views on use of samples by different entities:

Public willingness to donate biosamples, views on donation of different biosample types, and conditions of their use (by which organisations and for which types of research) are reported elsewhere (Public views on the donation and use of human biological samples in biomedical research – a mixed methods study, 2013, unpublished manuscript).

Participants were not informed about industry involvement in the study; the PIS states only that the University of Manchester and Genetic Alliance UK (a
charity) were involved. This could amount to an undeclared conflict of interest.

We did not specify the funders of the study in the PIS as we did not want to influence the comments participants made in any way during the focus group discussions, particularly around industry itself, i.e. they may have felt that they should be more positive towards industry than they otherwise would have, particularly because they were being paid to attend. Industry involvement in the project was highlighted on the STRATUM page of the Genetic Alliance UK website and on the STRATUM website itself if participants had been keen to find out more information about the project, and participants were asked if they had any questions before the groups discussion began. Moreover, Genetic Alliance UK was chosen to lead on the public engagement workpackage as they are an independent patient organisation whose membership is solely patient groups. Genetic Alliance UK exists to work on behalf of their members.

This is an important study on the attitudes of the UK public to biobank donation and consent. On the whole, it is well-conducted. However, there are a couple of issues relating to the study's industry funding and reporting of its industry-related results. First, the PIS did not mention industry involvement in the study, which it clearly should have done. Second, both the focus groups and the survey included questions regarding participants' view on different entities handling donation. The results of these questions are not reported in the paper, which is rather suspect given that Appendix V indicates that people trusted industry less than other entities. It appears that industry involvement was hidden in recruitment to the study and that results unfavourable to industry have been omitted, which is unfortunate. These results should be reported and discussed. Another limitation of the study mentioned: it did not examine how people's views on consent and data linkage might vary according to which entities the data is to be shared with.

The first two issues have been addressed in the responses above. The third point has now been addressed by highlighting this issue as a limitation of the study.

Other comments:
1. It should be stated how many participants were in each focus group.

We have addressed this point by adding the following statement:

There were seven participants in each focus group apart from the 18-25 age group and high SEG group (eight participants in each); serious/chronic illness group and healthy volunteers group (six participants in each) and the pilot group (five participants).

2. Why were there no participants from Wales or NI for the focus groups?

As each focus group was made up of a particular demographic group (e.g. low SEG; over 60 years etc) the main aim was to ascertain the views of people from that particular demographic rather than the views of people from that particular geographical area. Moreover, we were unable to cover all the home nations due to limitations of where the company recruiting participants had resources.

3. It is not stated whether survey respondents were paid; the assumption is that they were as they are "recruits" of a survey company. This should be clarified. The size of the honorarium for focus group members should also be stated. (It is possible that focus group members gave more "cooperative" responses than survey participants because they were paid (or paid more).)

We have added the following detail to the manuscript:

Each survey responder received a small payment (around £2) from Research Now.

Each focus group participant received £50 for taking part to cover time and travel costs.

We asked each participants at the beginning of each focus group to answer the questions honestly and that there were no ‘right’ or ‘wrong’ answers (see Appendix III). It was hoped that this would minimise the risk that they would try and give ‘cooperative’ answers, although we acknowledge it is difficult to prevent this completely.

4. A power calculation should be provided for the survey sample size.

5. The results section should also provide data on the survey results for the importance of consent and focus group results on preferred methods; at present only survey results on methods and group results on importance are included.

Apologies, this wasn’t very clear in the manuscript. We have amended the paragraph to make clearer the survey results for the importance of consent:
The majority of survey participants believed that obtaining consent for the use of residual biosamples was either extremely important (55%) or important (25%). Only 4% selected ‘not at all important’. Focus group participants also saw the consent process as important and cited reasons including....
Due to time constraints we were unable to discuss preferred methods for consenting with focus group participants. We have clarified this in the text:
This issue was not specifically addressed with focus group participants due to time constraints.

6. The definition of an ethics committee is slightly misleading as they normally only have lay representatives as members, not patients.

We agree that perhaps lay representatives rather than patients would have been a more accurate description. However, we are aware that in some cases ‘patients’ are on the committee. In addition, many lay people will have been patients at some point in their lives.

7. It is interesting that participants favoured an "active choice" over a "passive choice", but it is not clear exactly what they meant. This should be discussed further, as it could be argued that all choices are active regardless of how they are communicated.

We have clarified this point further:

an active choice whereby participants had to act on a decision to take part was preferable to a passive choice whereby consent was assumed;

8. Similarly, it is interesting that participants said that "opt-in" is truly informed consent. The information provided to potential donors is what guarantees that consent is informed; this is a different issue from the actual consent mechanism. While participants might not have realised this, it should at least be mentioned in the discussion.

This is an interesting point which we have added into the discussion:

It was also perceived as being truly informed consent by some participants (although it is worth noting that it is the information provided to potential donors that guarantees consent is informed rather than the consent mechanism).

Reviewer: Karoliina Snell, DSocSc, Post doctoral researcher Biomedicine in Society (BitS) Research Platform Department of Social Research University of Helsinki Finland

No competing interests

For methods of analysis: There are many terms (broad, narrow, blanket, dynamic...) for different types of consent. I would like to have a short explanation: why these particular terms (generic, tiered, specific) and the respective definitions were chosen? Where are they derived from - i.e. UK practice, some report?
Consent terms were selected based on common usage within the UK biobanking system (for example, generic consent is the term used by the Human Tissue Authority, National Research Ethics Service, and National Cancer Research Institute) and definitions chosen in consultation with a team of representatives from universities, hospital biobank staff, pathologists and industry. It was necessary to select and define one term per category to avoid the confusion inevitable when people use different terms for the same thing, or use the same term but mean something different. This can be a common problem in biobanking discussions. We chose and defined each consent term and piloted these definitions to ensure they were clear and understandable.
We have added an explanation about how we chose and defined each consent term as a footnote under Table 1. We have added:

Note: Consent terms were selected based on common usage within the UK biobanking system (for example, generic consent is the term used by the Human Tissue Authority, National Research Ethics Service, and National Cancer Research Institute) and definitions chosen in consultation with a team of representatives from universities, hospital biobank staff, pathologists and industry.

Within Table 1 we have also included the alternative terms frequently used within the literature.

Results are discussed in light of previous evidence, but the literature could be broadened. There are for example European comparisons (i.e. Eurobarometer 341) that would contextualize attitudes in UK to European trends. And also numerous other national case studies i.e. Valle-Mansilla (2010) Spain; Ursin et al. (2008) Norway, Sweden, Denmark; Ducournau & Strand (2009) France - that either make a good comparison or provide information about the meaning of informed consent to people. This latter point could be developed a bit further in the article.

We have added the following further evidence in the Discussion:

A study conducted in Sweden found a similar percentage of the general public were happy to agree to generic consent (67%), whereby surrogate decisions were performed by a research ethics committee[Hoeyer 2004]. Other national studies have found the acceptability of generic consent

amongst the general public and in particular patients to be higher, between 79%-95%[Wendler 2006,McQuillan 2003; Hoeyer 2005; Stegmayr 2003; Malone 2002].

In a pan-European survey, the majority of the UK public also preferred specific consent for every new study, although the percentage that did was slightly lower than the overall European average (65% compared to 67%)[Eurobarometer 341]. It was, however, higher than in Denmark and Finland, where the percentage of people who wanted to be re-contacted for every new study was lower at 51% and 54% respectively. These countries were also found to have very few concerns about the collection of personal information by biobanks and had high levels of trust in ethics committees. Other empirical work conducted in the USA, Canada, Sweden and Spain has shown that public preference is for generic consent[Murphy 2009; Simon 2001;Kettis-Lindblad 2007,Master 2013; Valle-Mansilla 2010].

Regarding the meaning of informed consent, we have added the following:

The preference for opt-in consent identified in the survey is consistent with the results of other studies in this area[3,15,16]. One reason for this preference may be that it matches the current system for organ donation for transplant in the UK. It was also perceived as being truly informed consent by some participants (although it is worth noting that it is the information provided to potential donors that guarantees consent is informed rather than the consent mechanism).

Was there a difference between patients and "non-patients"? This was not reported in the article? In our study, we found interesting differences and similarities between patients and citizens. Tupasela & Snell: "National interests and international collaboration" in New Genetics and Society interesting as it is also a mixed methodology study (survey, focus groups & interviews).

We did not find any significant differences between patients and non-patients or people who had had tissue removed and those that had not in the survey regarding their consent preferences. However, our results showed, interestingly, that all the people in the focus group which comprised people who were affected by an illness or disability preferred generic consent over tiered or specific consent. Hence, we have added the following sentence in the findings regarding generic consent:
It was also the consent model favoured by all participants who were affected by an illness or disability.

We have also added the following sentence in the Discussion section:
Focus group participants affected by an illness or disability were also found to prefer generic consent, and is likely to reflect the fact that patients have greater interests at stake [Tupasela & Snell 2012].

VERSION 2 – REVIEW

REVIEWER	David M Shaw, Institute for Biomedical Ethics, University of Basel, Switzerland. No competing interests. Bernice S Elger, Institute for Biomedical Ethics, University of Basel, Switzerland. Cemter for Legal Medicine, University of Geneva, Switzerland. No competing interests.
REVIEW RETURNED	02-Jun-2013

THE STUDY	The authors state that the results concerning distrust of industry will be reported elsewhere. It would be good to know which journal these results have been submitted to, in order to ensure that any negative results are not "buried".
REPORTING & ETHICS	In response to our comment that participants were not informed about industry participation, the authors reply that "We did not specify the funders of the study in the PIS as we did not want to

	influence the comments participants made in any way during the focus group discussions, particularly around industry itself, i.e. they may have felt that they should be more positive towards industry than they otherwise would have, particularly because they were being paid to attend." This response is not really satisfactory, as some participants might not want to have participated in an industry-funded study in the first place. This cannot now be helped, but should be taken account of in future studies.

VERSION 2 – AUTHOR RESPONSE

The paper reporting the results concerning distrust of industry has also been submitted to BMJ Open and is currently being re-reviewed following some minor revisions. If accepted, ideally we would like both papers printed in the same edition of BMJ Open. We will therefore change the reference (cited in this first paper) prior to publication to make this clear. At present, because this second paper has not yet been accepted, we can only cite that the paper has been submitted (which we do at the end of the Introduction).

Regarding the point that participants were not informed about industry participation, we take on board the reviewer's point that some people may not have wanted to participate if they had know this and if a similar circumstance arrises in another study, will ensure this information is provided in the PIS.