Reviewer's report

**Title:** An Implementation Framework for the Feedback of Individual Research Results and Incidental Findings in Research

**Version:** 4  **Date:** 22 July 2014

**Reviewer:** Pieter Hendrik Jan H Riegman

**Reviewer's report:**

This manuscript deals with the very difficult and complex subject of feedback of results after human biological materials have been used for medical research. It is based on the experiences gathered around a large study at McGill University Health Centre. Although the authors have a large international experience with different studies in different environments, the conclusions and even the procedures fit this study as well as the Canadian situation very efficiently, whereas the authors present the outcome as a generic solution for all studies on human biological materials. This brings me to the first revision:

**Major compulsory revisions:**

1. Present the study as the best solution for this study and the situation in Canada. The situation everywhere else is too diverse to present this as the way to go. It is rather a way the authors were able and wanted to go, which others might see as an example in this minefield. Not everybody would want or is even able to make the same choices due to the huge risks involved.

2. An important ethical line is crossed and it is actually nowhere mentioned. For many in the field feedback of IRR can only take place if the laboratory and the test both comply to the rules of an in vitro diagnostic lab / test. In Canada that probably means CLIA certified, or other countries CAP/ISO with a focus on not swapping or contaminating samples or sample derivatives in the chain of events in the pre-analytical and analytical phase. It is on the other hand mentioned on page 14 Just above the Keyholder Guidelines: “Finally, both the participant and/or the designated physician that is contacted may need to be informed of the possibility of false positives due to an inaccurate test result or a coding error during re-identification.” This is something you might do with an IF, but not for IRR. Always, the test needs to be repeated in an IVD setting and the test has to be properly validated before the results can be seen as robust. An important message with immediate life altering consequences coming from IRR must be based on robust results derived from an IVD lab and a properly validated test. Perhaps the sequencing lab in the study already has these qualities, but there are many studies using different tests that do not give a robust result and therefore cannot return results. This should be added as a requisite to the list of conditions when to return research results.

3. It would be nice to see some more transparency also from those bringing forward the arguments in the reason why there is a duty to feedback results. The reason why such studies wants to feedback even research findings is simply to
make it more interesting and worthwhile in the eyes of the participants and get more volunteers. That is fine, but then the consequences for the test and the laboratory need to be accepted and implemented as well. Although the authors want to bring IRR and IF as equal there is a difference here that needs to be described.

Minor compulsory revisions:

1. In the text on page 4 there are references to sections 1 to 4 that probably are remnants of an older version. After some time I could discover that the underlined italic headings follow the sequence of the Sections referred to however there seem to be added a 3b and 3c. Also the Discussion heading seems to be placed in later, because some subjects do not really feel like they are belonging under this heading.

2. The authors wanted to present this as an international framework for others to follow. It is clear that my advice would be not to do that. However, if so, the typically Canadian abbreviations should be declared in more international terms when first used i.e. REB. In addition, are the Canadian rules / recommendations accepted internationally.

3. The scope of studies where such a framework would fit, because the framework with the recommendations given would not be applicable to any study on human biological materials. For instance: In the keyholder guidelines number 3 it is suggested that the keyholder should be a physician, there can be situations where this is not desired and practical at all. There can even be situations where the can be database driven (TTP solution) and depends on the role an actor has acquired in the system with the permissions granted. In addition, in institutional matters it can even be non-medical personnel involved in collecting and procuring the samples for diagnostic reasons with access to the clinical data who can provide a researcher in a coded way of the latest follow-up data. The decision to provide feedback or not should in such cases be placed in the hands of a physician later in the chain. Therefore, it is needed where possible either to clearly provide the boundaries (type of study and countries) where these recommendations, conclusions and procedures might fit or present this as efficiently designed to this study and specific country, which could serve as an example for others who are able to use it or parts of it.

4. A major problem is to my view also to rely on scientists to discover IF’s, whereas the scientists are also not allowed to have more data at hand then necessary for the study, therefore they cannot judge properly. This point is described however, a scientists usually focusses only on his study field and therefore can easily miss other possible IF’s. He is not trained for that can blamed later on not having informed the donor (he should have known), whereas the donor counts on this when the study management promises this feedback. The latter is not mentioned.

5. The authors worry about the non-practicality of having some data not readily available and see this as drawing away funds from the study. I wonder if they already calculated the extra costs involved when the study promisses to provide feedback of IRR.
6. There are sometimes repeats in the text that might be avoided when putting certain parts together. In addition the story line seems sometimes not very logical.

7. Usefulness of the appendix might be questioned and perhaps left out completely.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

'I declare that I have no competing interests'