From: Chetkowski, Ryszard
Received via Email: January 25, 2008
Subject: CDPH Revised Draft Reporting Forms for hESC Research and Oocyte Retrieval

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The reporting form implies that all patients with severe OHSS grade A are treated as outpatients while those with grade B are inpatients, and that the difference between grades A and B is based on lab results. Actual clinical management is usually dictated by severity of symptoms not blood test abnormalities. In fact clinicians frequently avoid getting blood tests because they look so scary. Outpatient para/culdo-centesis is a frequent and effective temporizing treatment for all grades of severe OHSS. In some cases repetitive para/culdo-centeses are done without hospitalization. Inpatient monitoring has become infrequent except for grade C OHSS. Therefore, the form should include drainage of ascites regardless of where this procedure is done. Hope this is of help.

Richard Chetkowski, M.D.

From: Susan Berke Fogel
Received via Email: January 31, 2008
Subject: Comments on Ooctye retrieval forms

To Whom it May Concern,

Please accept these comments on the proposed Oocyte retrieval and SCRO forms on behalf of the Pro-Choice Alliance for Responsible
Research:

1) Thank you for addressing some of the concerns that we had raised pertaining to prior versions of these forms.

2) Re: SCRO Oversight Form:
In questions 6 & 7, we were not clear if oocyte donors for the fertility of others are actually considered "IVF patients/clients" for the purpose of these questions. That should be made clear, and we suggest that these two categories be separated:
6.1 female IVF patients/clients
6.2 oocyte donors specifically for fertility
6.3 Female donors Specifically for Research . . .
6.4 Other

3) Re: Written Record of Subjects Involved in Assisted Oocyte Production:
We note that all of the informed consent, conflict of interest disclosure, and research information requirements of SB1260 have been removed from the form. We would recommend that those elements be retained from earlier versions. We would also like to ask how the Department of Public Health intends to enforce those provisions if they are not reported.

Thank you for this opportunity to comment.

Cordially,

Susan Berke Fogel, J.D.
Pro-Choice Alliance for Responsible Research

From: Steven Peckman
Received via Email: February 1, 2008
Subject: COMMENTS on Revised HSCRAC Forms

Dear Human Stem Cell Research Advisory Committee (HSCRAC),

Please accept my late comments on the proposed reporting requirements and forms intended to fulfill CA Health & Safety (H&S) Code statutes for non-CIRM sponsored human embryonic stem cell (hESC) research. I appreciate the important work the Committee has performed. The seriousness and depth of discussion reflected in the transcript of the December 5, 2007 HSRCAC meeting was impressive as were the comments submitted by the other academic institutions that will be responsible for implementing the new stem cell regulatory requirements.

The transcript of the December meeting appears to highlight different perceptions of the HSCRAC members regarding the burdens of the proposed requirements/forms and the utility of the resulting data. There appeared to be a split in the HSCRAC between members who participate in the work of Stem Cell Research Oversight (SCRO) committees and those members who bring a more conceptual or abstract view of the requirements.

I continue to support the previous comments provided by Dr. Michael Kalichman (UCSD) and the Stanford University SCRO and would like to provide the following additional comments:

A. Ensure that the forms comply with the H&S Code and do not exceed the statutory requirements.

B. Ensure that the forms and requirements do not place an undue burden on SCRO committees, investigators, and institutions hosting research.

C. Ensure that the forms and requirements provide data in a form that is necessary and appropriate, in order to facilitate the future use of the information as contemplated by the legislature.

D. SCROs or SCRO like committees have been convened for several years at various California academic centers. SCRO administrators and members could bring a level of practical expertise and inform the HSCRAC decision making process. To this end, the HSCRAC should consider convening a panel of SCRO experts from various California institutions to discuss with the HSCRAC the potential ramifications of the proposed requirements and the potential of the requirements to unduly burden and overwhelm the local review system.

E. In recent years, many organizations have examined the negative impact of the bureaucratic burden in the IRB and IACUC process. The proposed HSCRAC requirements go well beyond any current State or Federal protections for human or animal subjects. The HSCRAC should consider whether it is necessary and appropriate to create new and unprecedented bureaucratic reporting hurdles that could result in overburdening a nascent research area thus making it increasingly difficult to conduct the research.

Specific concerns about the forms and related procedures:

1. The non-Assisted Oocyte Production (AOP) form:

a. Individual reporting of non-AOP projects will create a significant and undue burden on SCROs, the institutions they represent, and the research community without clear benefit to California, and is not a stated or implied requirement in the regulation (H&S Code 125119.3): "Each [SCRO]...shall report to the department, annually, on the number of human embryonic stem cell research projects that the stem cell research oversight committee has reviewed...." Therefore, the SCRO non-AOP form should only request aggregate numbers rather than reporting on individual projects.

b. The burden of individual project reporting will make it very difficult to administratively support SCROs as well as increase the bureaucratic burden on investigators. It is important to note that individual project reporting could result in overwhelming the current limited administrative support provided to SCROs. The proposed reporting requirements will likely: (1) require the extraction of data from specific investigator applications to comply with the individual report requirements, (2) require re-tooling of existing SCRO application forms to meet the new HSCRAC reporting requirements in order to collect specific data that may not be currently provided by investigators in a form easily translated to HSCRAC requirements (this is not a small effort), and (3) create an undue burden on an investigator community already overwhelmed by compliance reporting requirements. Ultimately, regardless of whether the HSCRAC believes individual reporting is necessary or valuable, such an expansion of the current statute should go through the appropriate legislative process.

c. Section 2.1 was not contemplated by the legislature and is not supported in the statute. The information requested is difficult to project and will not provide meaningful data to the legislature.

d. Section 3 was not contemplated by the legislature and is not supported in the statute. The requirement for the inclusion of such information places a tremendous burden on SCRO administrative staff, as the section requires extensive data entry. Not all SCROs have electronic submission capabilities and will have to manually enter the data. Additionally, the information provided in the reports will be interpretative, not very specific, and open to a broad range of variation.

e. Sections 4-7 were also not contemplated by the legislature and are not supported in the statute.

f. I again suggest that the HSCRAC consider my previously submitted form as a model that will fulfill the requirements of the letter and spirit of the statute in a format that SCROs and investigators will likely readily use without increased burden.

2. The AOP form:

a. The requirement that the AOP facility complete the form appears inconsistent with the statute. The statute requires that "A research program or project that involves AOP or any alternative method of oocyte retrieval shall ensure that a written record is established and maintained to include, but not be limited to, all of the following components". An AOP facility providing oocytes for an investigator is not necessarily a "research program or project". Consistent with the H&S Code, the process for completing the form should be left to the policy of the SCRO/IRB of record rather than dictated by the HSCRAC.

b. The H&S Code 125342(a)(3) requires the research program to maintain a record of "...all adverse health outcomes, including, but not limited to, incidences and degrees of severity, resulting from the AOP or any alternative method of oocyte retrieval." You will note that the Code does not require the reporting of such data at an individual level as suggested by the draft HSCRAC forms. Rather the code appears to require demographic aggregate reporting that would not compromise the confidentiality of the donors. The form should be modified accordingly.

c. Though the data required in the Subject Information section (2.1-2.7 and 6-10) may be consistent with the statute, the requirement to report individual donor demographic data combined with the information under "Oocyte Retrieval Information" may be in conflict with H&S Code 125342(b)(1)(a): "The information included in the written record pursuant to subdivision (a) shall not disclose personally identifiable information about subjects, and shall be confidential and is deemed protected by subject privacy provisions of law." The required reporting of the specific individual data sets should be assessed by qualified experts (external to the DHS) with in-depth knowledge of confidentiality procedures and demographic research to ensure that the requested data will not result in inadvertent identification and potential additional risks for donors.

To paraphrase Dr. Michael Kalichman's November 30, 2007 comments to the Committee: though it is possible the requested data in the draft forms may serve some research purpose, such a project should be designed and conducted by researchers rather than incorporated into reporting forms created to meet a regulatory responsibilities.

Thank you for considering my comments. Please do not hesitate to contact me if you have any questions.

Sincerely,

Steven Peckman

Associate Director
Eli and Edythe Broad Center of
Regenerative Medicine and Stem Cell Research University of California, Los Angeles

From: Michael Kalichman
Received via Email: February 2, 2008
Subject: COMMENTS on Revised HSCRAC Forms

To: Human Stem Cell Research Advisory Committee (HSCRAC),

I apologize for sending this comment very much past the January 31 deadline. However, I hope that at least the spirit of this message will be of some use in your further deliberations about reporting requirements for hESC research not sponsored by CIRM. Although I am writing as an individual, I am reasonably confident that my views are consistent with those held at the Burnham Institute for Medical Research, the Salk Institute for Biological Studies, The Scripps Research Institute, and the University of California San Diego. My thoughts, in brief, are as follows:

1. It is clear that the reporting forms have been significantly revised following the previous round of comments. Those revisions are greatly appreciated and appropriate. Based on a review of the transcripts of your meeting of 12/5/07, it is clear that you understood and responded to many of the submitted comments.

2. While the revised forms do require less information than before, it still seems that there are several areas in which significantly more information is requested than is necessary or appropriate to meet the legislative charge to monitor this research. Steve Peckman has nicely summarized many of the same concerns noted in the San Diego community, and he has correctly noted that the requested information reaches beyond a reasonable interpretation of the regulatory mandate while increasing the burden on the committees charged with reviewing this research as well as the investigators who are conducting the research.

3. In addition, one of the risks of asking questions on forms is that the reviewers of the resulting data may be misled into thinking they have learned something more than is actually the case. The potential problems for misunderstanding are numerous. For example, asking about "Anticipated Duration of Project from Last Review" might be interpreted by some institutions as the date for the next required *renewal* review, others as the date until the investigator must submit a *new* protocol to the Committee, others as the date that the investigator has projected for this particular study, others as the time-course required to produce a new therapeutic or diagnostic product, and finally others will note that research (and particularly this area of research) is changing so rapidly that predictions about duration are not feasible. Another example of concern is the proposed "Brief Summary, Description or Abstract of Research Project" Much of the current research is highly specialized and basic, requiring molecular, genomic, proteomic, cellular, or informatic approaches that are challenging even the expert reviewers of these projects. To the extent that summaries of such research are now being collected by review committees, these summaries are highly variable in length and clarity, but few of them will be readily accessible to the lay public. This isn't to say that investigators shouldn't develop the skill to explain their projects in simple terms, but this isn't something that our San Diego review committees are now requesting, it is something new that would have to be addressed to the investigators, and the risk is great that the necessary simplification will result in an oversimplification. At best, this kind of request will result in many hundreds of project descriptions each year, a large percentage of which will either be unclear to those not expert in the particular area of research or simplified to the point of providing little information that is new or of interest.

4. A reasonable question to ask about each of the proposed reporting questions is: "Will providing this information realistically empower a reviewer of the forms to act in such a way that would protect citizens of California or avoid waste of taxpayer dollars?" These goals are important, but unlikely to be achievable by the mechanism of an annual reporting form. However, this doesn't mean that these two goals aren't achievable. In both cases, it's hard to imagine that either function could be met in any different way or any better than what is already in place with thorough scientific review to choose the most meritorious research projects, and ethical and regulatory reviews by Institutional Review Boards and Stem Cell Research Oversight Committees.

4. Finally, I want to echo Steve Peckman's suggestion of convening a discussion with those who are now charged with reviewing stem cell protocols. Only with that dialogue will it be possible to align the goals of the reporting requirement with the realities of what the SCRO and ESCRO Committees are currently seeing.

Again, I apologize for the lateness of these comments, but (among other things) we've had a particularly busy month for reviewing hESC research.

Sincerely,

Michael Kalichman
Co-Director, ESCRO Committee, UCSD
Director, UCSD Research Ethics Program
Director, San Diego Research Ethics Consortium

From: Stanford SCRO Panel
Received via Email: February 5, 2008
Subject: Revised Draft Stem Cell Research Reporting Forms

Dear Dr. Ahmad:

The Stanford University Stem Cell Research Oversight Panel ("Stanford SCRO" or "SCRO") appreciates the opportunity to comment on the Department's revised draft stem cell research reporting forms (HSCR1260-1, -2). We apologize for submitting these comments shortly after the January 31 deadline, but as communicated to your office, we felt it was important to have faculty input and external reasons prevented that last week.

We were pleased to see certain revisions to the forms that acknowledged earlier comments from the academic research community. However, we continue to be concerned that the reporting forms considerably exceed the statutory mandate, and if implemented, would impose greater burden than federal research reporting requirements, CIRM requirements, and any other state's hESC reporting requirements. We therefore respectfully ask that you give further consideration to many of the comments in our prior letter (dated December 4, 2007), and the well-articulated comments in the recent letters from U.C.L.A. and U.C.S.D. We support those comments, and in particular, Steve Peckman's proposal that the Department convene a working group with SCRO representatives to discuss how to meet the reporting requirements.

We wish to highlight three ongoing, particular concerns:
1. HSCR 1260-1: SCRO reporting should be limited to human embryonic stem cell research, as clearly specified by S.B. 1260, § 125119.3. Item 3 regarding other stem cell projects should be removed, as it is neither required nor meaningful as a number.

2. HSCR 1260-1: This form should be limited to the SCRO reporting requirements in the law (number of hESC projects reviewed, status, and disposition; and unanticipated problems, serious continuing noncompliance, and response). Egg donor reporting should be covered separately, as explained below. And, such reporting should reflect the law's exclusive focus on women undergoing egg retrieval solely for research (not requesting information about the institution's patients in IVF therapy).

3. HSCR 1260-1 and 1260-2: We strongly encourage the Department to permit institutions to report on projects and egg donation in the aggregate. The individual research project forms that the Department is proposing are burdensome, as explained by U.C.S.D. and U.C.L.A. And as clinicians and researchers, we are concerned that the individual subject forms that the Department is proposing for egg donors would compromise confidentiality because of the totality of information required for a likely small number of women at a specific institution (*e.g.,* date of retrieval, age, race/ethnicity, combined with detailed health outcomes).

We appreciate your consideration of these comments.

Sincerely,

The Stem Cell Research Oversight Panel of Stanford University