

## ANGELIA'S MEETING NOTES

**WHEN:** November 13, 2001 at 10am

**WHERE:** Chamblee 101 room 2103B

**WHO:** NCBDD (Lisa Garbarino, Diane Schendel, Tom Horn, Larry Wilkenson)

**NOTES:** The meeting was held to discuss a sole source program announcement (02006) for Danish Medical Research Council (DMRC). The issues discussed were: OMB Clearance to not abide by the Paperwork Reduction Act, I.R.B., Project Period, Award Schedule, 1267, last FY's supplemental funds, Suspense/Award Procedures and a missing Payment.

1) OMB Clearance- Diane has been in contact with OMB regarding not abiding by the Paperwork Reduction Act. They have not responded back to her as of yet. When she hears from them she will forward me there response for the official file.

2) I.R.B.- The DMRC's I.R.B. process is different. Their I.R.B. is in effect for the entire length of the project. The question is how can we set make record of this and meet our federal requirements?

3) Project Period- It has been requested that this grantee be allowed a five year project period instead of the 3 year period stipulated in the HHS Policy Statement.

4) Award Schedule- A copy of the award schedule was supplied to me by Lisa, who stated that it had been determined by NCBDD and the previous Grants Specialist.

5) 1267- A 1267 has been prepared and is in for signature.

6) Last FY's Supplement- Lisa stated she had not received a copy of the Notice of Grant Award for a supplement. Diane thought she may have received a copy.

7) Lisa provided me with a request set of procedures for handling suspenses for the center and award distribution procedures.

8) Voucher Payment #2 for FY01 is missing

### TO DO:

- 1) Talk with Virginia Talley regarding I.R.B. requirements
- 2) Check in to obtaining a waiver from HHS for a 5 year project period
- 3) Followup with program for the funding documents
- 4) During Budget Negotiations talk with grantee about Domestic Banking and Procedure to change the PI
- 5) Research Missing Payment

## **FOLLOWUP**

**WHEN:** November 15, 2001

**WHO:** Virginia Talley and Diane Schendel

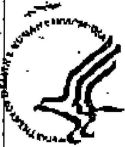
### **NOTE:**

Talked with Virginia Talley regarding the I.R.B. for Danish Medical Research Council(DMRC). Virginia stated that all grantees that accept Federal Funding must abide by Federal Laws. Thus DMRC must have their I.R.B. review human subject activities annually.

Talked with Diane and made her aware of my conversation with Virginia.

In addition on November 14, I talked with Dorimar Rosado regarding the Project Period. It was agreed that we would attempt to obtain a waiver and have a 5 year project period.

Angela Hill Gms



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service  
Centers for Disease Control

## Memorandum

Date November 30, 2001

From Team Leader, Developmental Disabilities Team, NCEH (F15)

Subject Review of Application in response to Program Announcement 02006

To Objective Review Committee Members

Exhibit 25

This memorandum will confirm your appointment to serve on the Objective Review Committee to review a sole source application in response to Program Announcement 02006, a cooperative agreement for Epidemiologic Studies of Reproductive and Developmental Outcomes-Denmark. We appreciate your willingness to serve in the formal review process that will result in funding the Danish Medical Research Council (DMCR). The Objective Review Committee is comprised as follows:

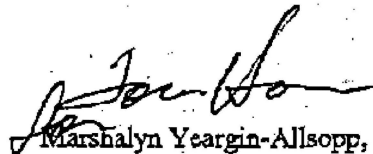
Lori de Ravellu, NCCDPHP - Committee Chairperson  
Cynthia Berg, NCCDPHP - Primary Reviewer  
William Thompson, NIP - Secondary Reviewer  
Jacquelyn Bertrand, NCBDDD - Secondary Reviewer

The committee will convene on Friday December 7, 2001, at 10:30 a.m., in the ground floor conference room (G-208) of Building 101 at the CDC Chambliss facility, 4770 Buford Highway.

Please review the attached guidance information which outlines the review process. It includes Program Announcement 02006, a description of the responsibilities of reviewers, and the evaluation forms. Panel members should be aware of their responsibilities as provided in these materials, and understand the overall mechanics of the review process. A technical review will be provided as soon as it is completed.

The steps in the objective review process, including procedures concerning voting and other related issues, will be reviewed when the committee convenes. If you have any questions in the meantime, please call Larry Wilkinson at 770-488-7211.

Thank you for your assistance.

  
Marshalyn Yeargin-Allsopp, M.D.

Attachment

December 10, 2001

From: Lori de Ravello  
Deputy Chief, SCR, NCCDPHP, CDC, (K21)  
Chairperson, Objective Review Committee, RFP #02006

To: José F. Cordero, MD, Director  
National Center on Birth Defects and Developmental Disabilities, CDC

Subject: Chairperson's Report on Review of Cooperative Agreement Application-  
Epidemiologic Studies of Reproductive and Developmental Outcomes - Denmark

The objective review committee appointed to review the cooperative agreement application for the above-noted Program Announcement 02006 convened on December 7 in the ground floor conference room G-208, Chamblee Building 101.

The objective review committee met to consider the proposal and render their final scoring and narrative comments to the Chairperson. Committee members participating as voting objective reviewers are listed in this memorandum.

Program staff from NCBDDD provided technical review comments to the panel, and were also available to provide programmatic and other information as requested by the review committee. Staff from the CDC Grants Management Branch (GMB) were in attendance during the review. A recorder was engaged to provide administrative support for the objective review.

Prior to the review, the committee members were provided copies of the application for which they were assigned as primary and secondary reviewers. They also received a copy of Program Announcement 02006; an overview of the objective review process; copies of the evaluation/rating forms for the application to be considered; and the schedule of the order in which the application would be presented, including designation of reviewers. Technical reviewer comments were made available to the appropriate objective reviewers before the committee meeting.

I introduced myself as the chairperson for this objective review committee and the Grants Management Branch representative and I discussed the committee's role - that of providing recommendations and advice to the Director, NCBDDD, as to the technical merit based on an assessment of the responsiveness of the application to the announced evaluation criteria. We then confirmed that all committee members had received all materials necessary for the review. I noted that the primary reviewer would be expected to present an oral evaluation, and secondary reviewers would present narrative comments. I indicated that an opportunity for discussion would follow the presentations and that program technical reviewers and grants management staff were available to respond to any questions raised by the committee. Then, following a motion to approve or

disapprove, the vote would be taken. Each approved application would be rated using the scale provided on the Reviewer Evaluation Form.

We informed the committee that should two or more members vote in the minority on a given application, they would be required to document their views in writing and that completion of the Reviewer Evaluation Form with detailed comments would suffice as the minority report. However, there was no occasion for using minority reports during this review.

Cynthia Collins from the GMB provided forms to all the reviewers on conflict of interest and obtained their signatures, confirming the acknowledgments of the policy regarding avoidance of a conflict of interest. Individuals were informed to abstain from voting on applications where a conflict might exist.

A total of 1 applicant sought funding from this Program Announcement. This one applicant was approved. Attachment 2 in this packet is the panel's score of the application under RFP 02006. Attachment 3 contains the objective review summary statements of the application.

The program office has retained all copies of the evaluation/rating forms, which include the primary and secondary reviewers comments and scores, and technical reviewer comments. These are available to you as a basis for your consideration of NCBDDD recommendations and your funding decisions.

These individuals comprised the Objective Review Committee for RFP #02006:

Chair	Lori de Ravello, NCCDPHP	K-21
Panel	Cynthia Berg, NCCDPHP	K-23
Members	William Thompson, NIP	E-61
	Jacquelyn Bertrand, NCBDDD	F-15
	Diane Schendel, NCBDDD	F-15

Please contact me should you have any questions or need additional information on the objective review process for RFP #02006.

  
Lori de Ravello

**Wojcik, Joanne (CDC/CCHP/NCBDDD)**

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**From:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**Sent:** Tuesday, November 04, 2008 12:11 PM  
**To:** Horne, Tom (CDC/CCHP/NCBDDD)  
**Cc:** Wojcik, Joanne (CDC/CCHP/NCBDDD)  
**Subject:** Letter from PGO

**Attachments:** Denmark Program\_garanti for opsigelse\_2005.pdf

Hi Tom,

The Institute Leader at University of Aarhus has asked if we can give him another, updated letter (ie signed more recently) similar to the one attached. His main interest is in the reassurance in the last sentence of the first paragraph. Can we discuss?

Thanks, Diana



Denmark  
rogram\_garanti for op



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Centers for Disease Control  
and Prevention

APR 07 2005

Paul Thorsen, MD, PHD  
NANEA at Department of Epidemiology & Social Medicine  
University of Aarhus, Vennelyst Boulevard 6  
DK-8000 Aarhus C, Denmark

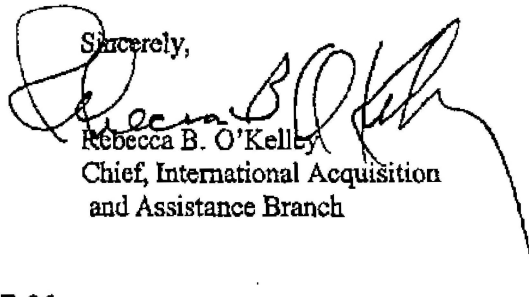
Reference: Cooperative Agreement No.: UR/CCU018305-06, Supplemental Request

Dear Dr. Thorsen:

This letter is in response to your supplemental request submitted to our office on March 18, 2005, for additional funding to cover potential termination cost. Potential liabilities or contingencies are not an allowable expense in accordance with the Office and Management Budget (OMB) Circular No. A-110, Section .60 entitled "Termination and Enforcement" which states "costs of a recipient resulting from obligations incurred by the recipient during a suspension or after termination of an award are not allowable unless the awarding agency expressly authorizes them in the notice of suspension or termination or subsequently." We cannot provide funding for potential liabilities or commit future funds to a potential liability, therefore your request is disapproved in the amount of \$340,519.00. We recognize that your proposed costs are in accordance with the Danish Law and if termination charges are incurred as a result of this cooperative agreement being terminated in accordance with OMB Circular A-110 referenced above charges would be paid when incurred.

We trust your program is progressing as planned. If you have any questions regarding this matter, please do not hesitate contacting Tracey Coleman, at (770) 488-2074 or fax (770) 488-2688 or e-mail address [TColeman3@cdc.gov](mailto:TColeman3@cdc.gov).

Sincerely,



Rebecca B. O'Kelly  
Chief, International Acquisition  
and Assistance Branch

Cc: Tom Horne, DBDDD, M/S E-86

## Exhibit 28

Wojcik, Joanne (CDC/NCBDDD/DBDDD)

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**From:** Schendel, Diana (CDC/NCBDDD/DBDDD)  
**Sent:** Thursday, May 18, 2006 8:34 AM  
**To:** Wojcik, Joanne (CDC/NCBDDD/DBDDD); Yeargin-Allsopp, Marshalyn (CDC/NCBDDD/DBDDD); Boyle, Coleen (CDC/NCBDDD/DBDDD)  
**Subject:** Denmark RFA concept  
**Attachments:** Denmark Concept RFA\_16May2006.doc

Hi folks,

Based on a series of exchanges with Don Lollar, I have modified the draft quite a bit. Mainly he suggested that I add more specific material about current and future activities to give more weight to the sole source argument (ie build up the breadth and depth of the existing program), and - because I was concerned that the discrepancy between what the grantee applied for (based on real funding) and what they potentially could apply for (based on announced funding) and the appearance of grantee not being responsive to the RFA - there is some wording in there for prioritizing, although no restrictions on upper limit of proposed activities (which allows flexibility in the grantees application without appearing non-responsive). The latter change is incorporated under Approach.

The result is much more lengthy, but it will be cut down in the review process I am sure. Hopefully, the section under Summary of Program will have the minimum language that will be retained.

Joanne, I am comfortable with you sending this on now.

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Thanks,  
Diana

5/18/2006

## Exhibit 29

**Wojcik, Joanne (CDC/CCHP/NCBDDD)**

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**From:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**Sent:** Monday, October 30, 2006 3:23 PM  
**To:** Garbarino, Lisa T. (CDC/CCHP/NCBDDD)  
**Cc:** Lollar, Donald (CDC/CCHP/NCBDDD); Smith, Joe (CDC/CCHP/NCBDDD) (CTR); Wojcik, Joanne (CDC/CCHP/NCBDDD)  
**Subject:** RE: Denmark RFA  
**Attachments:** Recom SEP Panel Members\_Denmark.xls

Lisa – attached are some suggested reviewers.

Thanks, Diana

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**From:** Garbarino, Lisa T. (CDC/CCHP/NCBDDD)  
**Sent:** Wednesday, October 11, 2006 2:51 PM  
**To:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**Cc:** Lollar, Donald (CDC/CCHP/NCBDDD); Smith, Joe (CDC/CCHP/NCBDDD) (CTR)  
**Subject:** RE: Denmark RFA  
**Importance:** High

the announcement is still at the department. if you could have names to me by the end of october that would be fine

**Lisa T. Garbarino**  
**Public Health Analyst**  
**Office of Extramural Research**  
**National Center on Birth Defects**  
**and Developmental Disabilities**  
**telephone: 404-498-3979**  
**fax: 404-498-3060**

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**From:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**Sent:** Wednesday, October 11, 2006 2:46 PM  
**To:** Garbarino, Lisa T. (CDC/CCHP/NCBDDD)  
**Cc:** Lollar, Donald (CDC/CCHP/NCBDDD)  
**Subject:** RE: Denmark RFA

OK – so its not too late (or, when do you need the names – last chance?)

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**From:** Garbarino, Lisa T. (CDC/CCHP/NCBDDD)  
**Sent:** Wednesday, October 11, 2006 2:37 PM  
**To:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**Cc:** Lollar, Donald (CDC/CCHP/NCBDDD)  
**Subject:** RE: Denmark RFA

11/1/2006

**Wojcik, Joanne (CDC/CCHP/NCBDDD)**

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**From:** Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP)  
**Sent:** Monday, April 20, 2009 12:26 PM  
**To:** Boyle, Coleen (CDC/CCHP/NCBDDD); Home, Tom (CDC/CCHP/NCBDDD); Wojcik, Joanne (CDC/CCHP/NCBDDD)  
**Cc:** Floyd, Louise (CDC/CCHP/NCBDDD); Bertrand, Jacquelyn (CDC/CCHP/NCBDDD); Denny, Clark (CDC/CCHP/NCBDDD); Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP)  
**Subject:** RE: Reg. 5 U10 DD000230 - DD07-001

Good afternoon,

For your information, I am forwarding Anne's official notification indicating Poul Thorsen's resignation from the university and the project. She further indicates that project activities are on hold until the Co-PI situation is resolved.

Nassi

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**From:** Anne Christiansen [mailto:anch@fi.dk]  
**Sent:** Sunday, April 19, 2009 8:58 AM  
**To:** Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP); Williams, Randolph B. (CDC/OCCO/PGO)  
**Subject:** Reg. 5 U10 DD000230 - DD07-001

Dear Nassi & Randolph,

With this email I wish to officially confirm that co-principal investigator Poul Thorsen has resigned from his position at University of Aarhus. Consequently, research activities and spending of funds related to project year 3 (budget period 01022009 - 31012010) has been put on hold until a solution has been found with regards to the principal investigator issue.

Kind regards

Anne Christiansen

**Anne Christiansen**  
Head of Secretariat  
Grant Administration  
Direct Phone: + 45 3544 6374  
E-mail: anch@fi.dk

**Ministry of Science  
Technology and Innovation**

Danish Agency for Science, Technology and Innovation  
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Fax: +45 3544 6201  
E-mail: [dasti@dasti.dk](mailto:dasti@dasti.dk)  
[www.dastl.dk](http://www.dastl.dk)

5/2/2009

Down syndrome-Denmark Conference Call  
December 11, 2009

Participants: Henrik, Diana, Adolfo, Jan, Liang, Sonja

1. Discussion of tables/figures sent to us by Liang
  - a. Table 3.3 needs to have additional covariates added – (1) +/- congenital heart defects, and (2) +/- congenital GI defects (we initially discussed looking at any congenital non-cardiac defects, but Liang told us that the rate of these defects was very high, so we decided to limit this to congenital gastrointestinal defects – e.g., duodenal atresia, imperforate anus, Hirschsprung disease, etc.). Sonja will consult with Henrik and Jan to get ICD10 codes that correspond to these defects.
  - b. We also discussed the need to include information on mosaic Down syndrome in Table 3.3 since that is the focus of the paper. Rather than using it as a covariate (given small numbers of cases in this category), we decided to stratify based on that mosaic/non-mosaic. See table shell below.
  - c. We discussed need to include mosaics (stratify by mosaic/non-mosaic) for Table 3.4 as well, given that mosaicism is the focus of the paper. It is recognized the numbers will be small in the mosaic category.
  - d. We discussed why 1990-1999 was the category used for referent for birth cohort analysis. Liang said that this was because there were small numbers of deaths in the 2000-2007 category -- when this group was used as a referent, the confidence intervals were wide. We discussed possibly using the < April 1, 1968 group instead.
  - e. It was proposed that an analysis by trend be performed on birth cohorts for both Tables 3.3 and Table 3.4 to show that trends are statistically significant (they appear that they would be).
  - f. We discussed that it would be helpful to know when surgery for congenital heart defects began being performed on infants with Down syndrome in Denmark. Henrik thought it was similar to the time when this began to occur in the US.
  - g. For the Figure 3.1A, it was proposed that we add the n's to the Figure Legend (number of persons with each type and then number of deaths).
2. Discussion of analysis of hospitalizations – table shells sent by Sonja
  - a. Discussion of Table 2 (hospital admissions by time at risk) – we discussed how “time at risk” should be determined. This time will need to take into account persons who died and those who moved away from Denmark. The issue for discussion was whether to exclude days that the person was hospitalized, since during those days, the person would not be “at risk” for another hospital admission. We decide to do this.
  - b. Liang asked which “Reasons for hospitalization” would be included – we decided to include the same “Reasons for hospitalization” that are listed in Table 3. Sonja has a list of ICD10 codes that correspond to these reasons

Wojcik, Joanne (CDC/ONDIEH/NCBDDD)

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**From:** Rasmussen, Sonja (CDC/ONDIEH/NCBDDD)  
**Sent:** Thursday, June 10, 2010 3:06 PM  
**To:** Wojcik, Joanne (CDC/ONDIEH/NCBDDD); Rasmussen, Sonja (CDC/ONDIEH/NCBDDD)  
**Cc:** Paradies, William A. (CDC/ONDIEH/NCBDDD); Honein, Margaret (Peggy) (CDC/ONDIEH/NCBDDD); Correa, Adolfo (CDC/ONDIEH/NCBDDD); Boyle, Coleen (CDC/ONDIEH/NCBDDD); Schendel, Diana (CDC/ONDIEH/NCBDDD)  
**Subject:** RE: Down syndrome-Denmark conference call - tomorrow (3/12) at 12:00 p.m. Eastern time  
**Attachments:** downsyndromesummary\_12182008.doc; Down syndrome\_3\_12\_2010\_sar.doc; Down syndrome\_2\_12\_2010\_sar.doc; Down syndrome\_12\_11\_2009\_sar.doc; Down syndrome\_11\_13\_2009.doc; Down syndrome\_10\_22\_2009.doc; Down syndrome\_09\_25\_2009.doc; Down syndrome\_6\_11\_2009.doc; Down syndrome\_Summary\_call\_5-15-09.doc; downdenmark\_04\_17\_09.doc; Down syndrome conference call\_2\_13\_09.doc; Down syndrome\_1\_23\_2009.doc

Joanne,

Here are call notes from our most recent calls. To be honest, I'm not sure how helpful they'll be since we are typically responding to tables or figures that Liang (or previously Claus) sent to us (they summarize our discussion of "details", not the "bigger picture"). But I've attached them so you can see what our discussions have been. You'll see that the two projects we've been discussing are survival and hospitalizations. We had one call where Henrik briefly discussed a study of cancer among persons with Down syndrome, but it wasn't clear to me that this study was part of the cooperative agreement – I have asked him to update us on the study and he has not taken me up on it.

Thanks.  
 Sonja

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**From:** Wojcik, Joanne (CDC/ONDIEH/NCBDDD)  
**Sent:** Thursday, June 10, 2010 1:46 PM  
**To:** Rasmussen, Sonja (CDC/ONDIEH/NCBDDD); Honein, Margaret (Peggy) (CDC/ONDIEH/NCBDDD)  
**Cc:** Paradies, William A. (CDC/ONDIEH/NCBDDD); Correa, Adolfo (CDC/ONDIEH/NCBDDD); Boyle, Coleen (CDC/ONDIEH/NCBDDD); Wojcik, Joanne (CDC/ONDIEH/NCBDDD)  
**Subject:** RE: Down syndrome-Denmark conference call - tomorrow (3/12) at 12:00 p.m. Eastern time

Hi sounds good. Coleen knows much more about this project than I do. I don't believe I've seen call notes from the Down Syndrome discussions, would you be able to share w/me?

Tx much

jw

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**From:** Rasmussen, Sonja (CDC/ONDIEH/NCBDDD)  
**Sent:** Thursday, June 10, 2010 1:43 PM  
**To:** Wojcik, Joanne (CDC/ONDIEH/NCBDDD); Boyle, Coleen (CDC/ONDIEH/NCBDDD); Honein, Margaret (Peggy) (CDC/ONDIEH/NCBDDD)  
**Cc:** Paradies, William A. (CDC/ONDIEH/NCBDDD); Correa, Adolfo (CDC/ONDIEH/NCBDDD)  
**Subject:** RE: Down syndrome-Denmark conference call - tomorrow (3/12) at 12:00 p.m. Eastern time

Thanks, Joanne, it seems like there are a lot of issues for us to discuss regarding this project. What is written below doesn't represent the status of the project. I don't believe Erik P, Nils, or Carsten Obel have participated in any of our conference calls (Carsten may have been on some calls, but he hasn't had any substantive role), so this may be why they're confused about what the projects and planned products are. In addition, we are not aware of plans to add Finnish or Swedish data to the cancer analysis, so I'm not sure if this is considered part of our funding – this has not been discussed with the CDC group. In addition, the date for end of funding is new – we hadn't previously heard that.

Peggy suggested that perhaps Monica could set up a meeting for you and Coleen to update me, Adolfo, and Bill and for us to update you on the project status. We also need to be sure that Liang (and the person that supervises Liang – do

Down syndrome-Denmark Conference Call  
November 13, 2009

Participants: Poul, Jorn, Henrik, Diana, Adolfo, Jan, Liang, Sonja

1. Discussion of tables/figures sent to us by Liang

- a. We had a long discussion of Figure 1.1. Henrik shared with us his discussion with a Danish Cytogenetic Registry staff member, who told him that "age at diagnosis" actually refers to when the testing is completed, not when diagnosis is actually made (given that this is a relatively easy clinical diagnosis in most kids). Henrik plans to talk with the head of the Cytogenetic Registry, but he is currently on holiday – he will discuss this issue with him when he returns. When a Robertsonian translocation is identified in a baby, parents' karyotypes are typically done to see if one of the parents carries the translocation; thus, "completion" of testing is often delayed. This may be why we saw the results that we did with Robertsonian translocations when the curves were left-truncated at age at diagnosis. We had an extended discussion of pros/cons related to using birth as the start point or age at diagnosis as start point for Kaplan-Meier curve. Using birth as the start time point has the advantage of being consistent with the fact that Down syndrome is present from birth (actually from conception); however, there are issues of immortal observation time. Using "age at diagnosis" is problematic though – Henrik expressed concerns that this might not be a variable that is valid. We discussed the possibility of doing some additional analyses to look at the potential impact of using birth rather than age at diagnosis. In the end, we decided to use birth as the starting point for the analysis; however, we will add a limitations section to the discussion that will address problems related to some infants possibly dying before the diagnosis of Down syndrome was made and how that might affect our analyses.
- b. We may be able to say something in the paper about the effects on stratifying on age at diagnosis (results shown in Figure 2); however, decision on this will be made after Henrik speaks with head of Cytogenetic Registry.
- c. We will begin writing the manuscript describing this analysis. Plans are to include Figure 3A in the paper, as well as Tables 3.1 and 3.2 (these include comparison to the general population).
- d. Additional analyses to be performed:
  - i. We would like to look at the effect of certain factors on survival (other than karyotype) – including Sex, Birth Weight, Presence/Absence of Congenital Heart Defect, Presence/Absence of Other Congenital Non-Heart Defect, and Birth Cohort. Adolfo noted that we may want to look at Birth Cohort as an effect modifier. Jorn also asked Liang to look at proportional hazard ratios by age to see if these differ. Liang will work on these

analyses for our next call.

- e. Sonja will begin working on writing up a manuscript describing this work. Poul offered to help with this process.

- 2. Our next call will be **12/11 at 12 noon Eastern time**. On this next call, we will try to complete the discussion of analyses for the survival paper – then we will begin working on the hospitalizations analysis.

Thanks!

Sonja

Down syndrome-Denmark Conference Call  
October 22, 2009

Participants: Liang, Nils, Adolfo, Sonja, Diana, Poul

1. Discussion of tables/figures sent to us by Liang

- a. Previously, all comparisons were made between persons with Down syndrome by karyotype. Part of the reason for this was because at the time we started this project, we did not have data on the general population of Denmark. Jan had suggested that it would be good to compare Down syndrome (standard trisomy 21, Robertsonian translocation, and mosaicism) to the general Danish population. Liang will talk with Henrik about whether he has access to the data we'd need to compare survival among these Down syndrome karyotypes to the general Danish population.
- b. Much of the discussion focused on concerns about Figures 1 and 2:
  - i. The results for Robertsonian translocations were very different from what we observed previously (see poster that Claus presented at the 2008 American Society of Human Genetics meetings).
  - ii. Biologically, there is no reason to expect why persons with Robertsonian translocations would be more severely affected than those with standard trisomy 21.
  - iii. Causes of death for these two groups (Table 11) look generally similar, as would be expected.
  - iv. The results summarized in the figures (and in Table 6) seem to be inconsistent with what is presented in Tables 8 and 10, where there seems to be little difference between survival among persons with standard trisomy 21 and with Robertsonian translocations (adjusted hazard ratios are 1.04-1.07) – the figures and Table 6 imply a much greater difference in survival.

The plan is for Liang to discuss with Claus and try to figure out why these results are so different. Other thoughts to follow up on this issue were (1) to look at survival from birth using age at diagnosis as a covariate or stratifying variable, (2) to look at the distribution of age at death for the three karyotypes, and (3) to stratify by age at diagnosis (looking separately at those diagnosed < 1 year or < 6 months).

Liang will send us what he finds after his discussion with Claus for our review before deciding which of these to pursue.

2. Next call: We did not schedule another date for our next call since so many were unable to participate today. Sonja will send an e-mail looking for dates for the next call and will pick the date the works for the most people.

Thanks!  
Sonja

Down syndrome-Denmark Conference Call  
September 25, 2009

Participants: Soren, Liang, Nils, Claus, Jorn, Adolfo, Sonja

Unable to participate today but involved in project – Jan Friedman, Henrik Hasle, Diana Schendel, Poul Thorsen

1. Introductions – all participants introduced themselves and discussed their role in the project. Liang will be taking over from Claus as analyst for this project – he will be working full-time on these studies.
2. Discussion of study on survival among persons with Down syndrome by karyotype
  - a. Sonja introduced the study, the status of the analysis, and issues that yet need to be considered.
  - b. The plan for this analysis is to look at a Kaplan-Meier survival curve by karyotype for persons with Down syndrome in Denmark. Of note, Henrik, Jan and Sonja have been working to be sure that all cases are appropriately categorized into the right karyotype (full trisomy, Robertsonian translocation, mosaic) and this categorization has recently be finalized. Henrik has the most recent file on patients in the study. Liang will need to get this file from Henrik.
  - c. In addition, the plan is to look at risk factors for poor survival using Cox proportional hazards model – factors proposed to be examined include sex, birth year cohort, congenital heart defects (present/absent), low birth weight (< 2500 g/>+ 2500 g), possibly other birth defects (present/absent).
  - d. We discussed the issue of mosaicism being more likely to be diagnosed later in life, presumably because people lose the extra #21 chromosome in some cells during mitosis. Thus, it's important to take into account age at diagnosis.
  - e. Jorn proposed that we look at survival from time of diagnosis, rather than from time since birth. Adolfo suggested that we take a look at the distribution of age of diagnosis of Down syndrome for the three categories. Jorn also discussed the need to look at trends in age at diagnosis of Down syndrome through the years. Liang will work on these analyses.
  - f. Another issue related to age at diagnosis is congenital heart defects. There is likely to be an earlier age of diagnosis of congenital heart defects over time, given increasing use of echocardiography. Sonja discussed the issue of the frequency of congenital heart defects being higher in the Danish cohort than in previous publications (~58% vs. 40-50% in previous studies). This is likely related to the inclusion of minor congenital heart defects (e.g., patent ductus arteriosus, patent foramen ovale), especially in more recent years.
  - g. Sonja commented that she has been unable to find an “official” cross-walk between ICD8 and ICD10 codes, which we will need to complete this and the hospitalization analysis. Jorn said he believes this does not exist, but

Liang or Li may have an unofficial list, which they will share with the group.

- h. Jorn mentioned that it may be possible to expand this analysis to other Nordic countries.
3. Discussion of study on hospitalizations among persons with Down syndrome vs. persons without Down syndrome.
  - a. Sonja introduced this study, the status of the analysis, and issues that need to be considered to move the project forward. The study is focusing on burden related to Down syndrome overall and by different age groups – burden will be assessed by number of hospital admissions and number of hospital days, and then what diseases are more likely to result in hospital admission among persons with Down syndrome, compared to persons without Down syndrome. Several table shells were sent to all attendees before the conference call. This study will focus on non-mosaic cases of Down syndrome (full trisomy and Robertsonian translocations included, mosaic cases will be excluded). Thus, Liang will need the latest classification of karyotypes from Henrik for this analysis as well.
  - b. For this analysis, we previously selected a reference group – 20 controls matched by years of birth cases with Down syndrome. The expectation is that these “controls” were randomly selected (other than based on year of birth). Liang will check to see if this appears to be the case by looking to see if these persons differ from official statistics in Denmark.
  - c. Jorn also mentioned that we could potentially use the entire Danish cohort – this could be obtained from Statistics Denmark and sent (anonymized) to Liang. We decided to check to see if the controls we have were randomly selected – if so, we’ll probably use these controls.
  - d. Covariates to be considered in the analysis of hospitalizations include birth cohort (year of birth), congenital heart defects (presence/absence), low birth weight (< 2500 g, >= 2500 g), sex, and where the person with Down syndrome lives (distance to hospital based on postal code where the family lives – probably 3 levels of proximity to the hospital). Sonja mentioned that a table shell with some of these covariates had been put together, but was not shared with the group. This table shell has now been inserted (below).
4. Down syndrome and cancer study
  - a. We will hold discussion of this project until a future conference call when Henrik Hasle (project lead) is available.
5. Sonja emphasized the importance of us completing these analyses and submitting manuscripts for publication within the next year. Liang is encouraged to send Sonja and others tables for review in between conference calls and to ask questions as needed. We discussed the possibility of CDC collaborators travelling to Denmark to work directly with Liang on the analysis – it is likely that this will be needed.
6. Next call – our next call will be Thursday, October 22, at 10 a.m. Eastern time. The conference call numbers remain the same as for previous calls:



Down syndrome-Denmark Conference Call  
June 11, 2009

Participants: Claus, Diana, Sonja, Poul, Jan, Adolfo, Henrik

1. Discussion about Tables sent to us by Claus –
  - a. Table 1 – recommendations to further break down low birth weight (e.g., < 1500 g and 1500-2499 g) and preterm gestational age (20-28 weeks, 29-32 weeks, 33-34 weeks, 35-36 weeks).
  - b. Table 1 – Birth weight and gestational age are only available for certain years. So as to not be misleading, I think we need to somehow include those as missing in the Table itself (not just in the footnote). For now, can we list for Birth weight “missing < 1973” and “missing 1973-2007” and for Gestational age “missing < 1978” and “missing 1978-2007”? (Of note, this comment was not discussed on the call, but I think we may have misread the table and thus we thought that a small number of cases had missing birth weights (0.1%, according to the table), whereas it appears that it's about half of the cases – same issue for gestational age).
2. Comments on Table 3 –
  - a. Column headings should be “Hospital days”, rather than “Hospital days by time at risk”
  - b. “Other neoplasms” should be just “Neoplasms”
  - c. We were unsure why we didn't see an increase in Mental and behavioural disorders in adulthood, given that Alzheimer disease is in this category. We will need to explore whether a person with Down syndrome for whom Alzheimer is suspected would get admitted to a hospital in Denmark, or if he/she would just receive outpatient treatment.
  - d. We will need a supplementary table that includes the ICD8/ICD10 codes that go with each “reason for hospitalization” – this could be made available online.
  - e. A supplementary table could also be made available online or in an Appendix for the number of hospital days among controls.
  - f. Under the column headings are numbers that represent the total person-days at risk. Instead of including this as part of the column headings, it was proposed that we list this as the first row of the table with the label for the row being “Total person-days at risk”.
  - g. Regarding the cases that had “Down syndrome” as their primary diagnosis, it would be helpful to check on two things related to this diagnosis. First, is there a secondary diagnosis listed in these cases, and second, of those under 1 year of age with Down syndrome as their primary diagnosis for the hospitalization, at what age were they admitted. The hypothesis is that these babies were diagnosed as part of their birth hospitalization -- we should be able to tell this because the date of admission should be equal to the date of birth.
  - h. The reasons for hospitalizations are all based on ICD10 codes, but for

earlier years, ICD8 was available. To use these older data, we need to understand how ICD8 translates to ICD10. Sonja will check to see if there is a crosswalk available.

- i. We decided that we could combine the two categories: "diseases of the eye and adnexa", with "diseases of the ear and mastoid process" to get "diseases of the eye, adnexa, ear and mastoid process"
3. Discussion of additional tables –
  - a. We discussed whether we would want to look at the entire tables with hospital admissions and hospital days by time at risk for persons with Down syndrome by reason for hospitalization by age group for different risk factors (e.g., presence of congenital heart defects, low birth weight, sex, etc.). We decided that this might be cumbersome and that it might be better to create a new table that has risk factors for hospital days by age groups. Sonja will work on drafting a table shell and send it around for comment. The risk factors that we discussed including in the Table were (1) birth weight (< 2500 g vs.  $\geq$  2,500 g), (2) sex (male vs. female), (3) Presence/absence of congenital heart defects, (4) Presence/absence of other major congenital defects, (5) birth cohort, (6) gestational age (< 37 weeks vs. 37+ weeks).
4. It would be helpful if Poul and Claus can come up with a timeline of when the Tables for the analysis of hospitalizations will be completed, so Sonja can communicate this to DBDDD leadership.
5. **Next call – our next call will be Thursday, July 9, at 11 a.m. Eastern time.**  
**The conference call numbers remain the same as for previous calls:**

Toll Free / Freephone: DENMARK  
USA (b)(6)

(b)(6)

Leader Passcode:

Participant Passcode

(b)(6)

**Summary**  
**Conference Call – May 15, 2009**

Participants: Claus, Jan, Diana, Henrik, Sonja and Adolfo (Poul not available)

1. Discussed table shells put together by Sonja, numbers added by Claus – Diana noted that the tables are pretty tight for space, with wrapping of numbers. We discussed that denominators could be listed at the top of each column, rather than being included in each row and that we could truncate the rate ratios and 95% CIs to leave just one digit after the decimal point. We will review again after these are done. Otherwise, tables look good. Sonja will send Henrik and Jan the ICD10 codes so we can decide which categories to lump and which should be individually listed in the table.
2. Claus raised issues related to the congenital heart defect (CHD) designation. This is complicated since our source of information on CHD will vary by time-period – Malformation Register for 1984-1994, National Patient Register for 1977-1984 and 1994-1997. We decided that this is an issue that we won't likely be able to get around – that we will need to list this issue in the Methods and then include this as a limitation in the Discussion.
3. We also discussed issues related to which cases to include in the study, based on cytogenetic analyses. There were two issues: (1) whether to include 47, +G, and mosaic 47, +G. Although we know that these could occasionally be +22, not +21, we decided that given the rarity of trisomy 22, both as mosaic and full trisomy, that it was okay to include all with +G (assume they are +21). (2) whether to include cases with additional chromosome abnormalities. We decided that if the additional chromosome abnormality was known to have a phenotype that accompanied it, we would exclude the case.
4. Given that Poul wasn't on the call, we didn't set a date for the next call. We will check on date by e-mail.

Thanks to all for participating!

**Summary**  
**Down syndrome-Denmark Conference Call**  
**April 17, 2009**

Participants: Poul, Claus, Henrik, Jan, Diana, Adolfo, Sonja

1. How to handle congenital heart defects (CHDs). One thought we had early on was to look at number of hospital admissions and hospital days (as Claus has done) for all persons with Down syndrome and then to divide it by those with and without heart defects – that information will be helpful, especially given that the data we've seen so far suggests that CHDs are a major contributor to hospitalizations for most age groups. Important questions for a person *without* a CHD (presumably ~ 50% of patients with Down syndrome) are (1) how often are they hospitalized (number of hospital admissions), (2) for how many days, and (3) what are their reasons for hospitalization. In the past, we've struggled with the fact that the information that we have on congenital heart defects suggests that the rate is higher than has previously been reported – we have wondered whether this is due to minor defects being included. I think we'll need to come to some sort of decision about how to identify cases with congenital heart defects. Another issue related to this is defining congenital heart disease prior to 1997 – before this was included in the Medical Birth Registry. Claus, have you gotten the data for before 1997 yet?

- Claus has gotten the pre-1997 data and will send it to us so we can take a look at data from this time period (% of cases with non-mosaic Down syndrome with/without heart defects overall and by year of birth) (similar to Table 5, but including pre-1997 data).
- There is the possibility of reviewing a sample of medical records with codes of congenital heart defects to determine whether the child truly has a congenital heart defect that is clinically significant (although it was noted that making this distinction, even with medical record review, may still be difficult). However, given the current issues with the Denmark project, we'll plan to go ahead with the data that we have on congenital heart defects, recognizing that at least in later years, this likely includes some patients with mild defects. Using the data that we presently have on presence/absence of congenital heart defects, we'll look at number of hospital admissions and hospital days overall and by reason for different age group in order to better understand the contribution of the presence of CHD to hospitalizations.

2. Right now, with all the age categories, we have a lot of tables. Another question is whether these age categories make sense or whether additional condensing of the categories would be appropriate. Current categories are <1, 1-4, 5-14, 15-29, 30-44, 45-59, 60+ (seven categories). One alternative would be <1, 1-20, 20-40, 40-60, 60+ (five categories) or <1, 1-10, 10-20, 20-40, 40-60, 60+ (six categories).

- We decided to change the age category breakdown to < 1, 1-4, 5-20, 20-50, 50+ years (5 age categories). With this change, we won't need separate tables for each age group, but instead should be able to put all age categories on one table for hospital admissions and another table for days of hospitalization, which will make comparison by age groups easier.

3. What categories should be on the "hospital admissions/hospital days" tables and how much breakdown of the categories should we include? Right now, I believe these are ICD10 categories, with some breakdown of the Q (birth defects) category – Claus is that right?

- We decided that we will need to lump these categories further – Sonja, Jan and Henrik will work on coming up with new categories and will share with the group.

4. What tables do we need for the hospitalizations paper? My thoughts are that we will need:  
-- Table 1: Descriptive table of cases and controls – right now, this would include Tables 1

and 2 in the pdf attached. Are there other factors that we could include on this table that would be helpful? Presence/absence of congenital heart defects might be one that could be included here. Other demographics – especially anything related to socioeconomic status – would also be of interest.

- We agreed to add maternal age at delivery and presence/absence of congenital heart defects to the table. We discussed adding other variables that could provide information on socioeconomic status, but decided not to do this at this point, given that we were unlikely to be able to use it in the present analysis and that it would require tapping data that is located at Statistics Denmark.

-- Table 2: General descriptive data for hospitalizations – I'm hopeful that we could include information on number of hospital admissions by risk time, and hospital days by risk time (and risk ratios and 95% CIs) for cases and controls in this table. Ideally, I think we would want to show this overall and with/without heart defects, but this could get to be a large table.

- We may be able to add these data as totals to the other two later tables – we would have one table with hospital admissions, by age group and total, and one with hospital days, by age group and total. As part of these tables, we will likely need "sub-tables" -- tables 2b and 2c and table 3b and 3c that will include presence/absence of CHDs.

-- Remaining tables showing reasons for hospitalization by age group (so number of tables defined by number of age groups – see question 2) – again, I was thinking that we could include both info on number of hospital admissions and number of hospital days on the same tables. And it would be of interest to look overall and with/without heart defects – but another big table!

- See above bullet.

5. We are making good progress on the results section of the paper – has there been any progress on the Methods section? I think Poul and Henrik were working on this?

- Henrik had sent this several months ago and Sonja missed it. She will incorporate it into the draft of the paper.

6. Henrik presented data from analysis of cancers.

- There are some differences in the total numbers between this analysis and that of hospitalizations. First, the cancer registry goes through 2006, so cases born after 2006 are excluded. Second, cases born outside Denmark are traditionally excluded from cancer registry studies. All were agreeable to doing this in our Down syndrome-cancer study as well.
- The SIR is adjusted for sex, age and time period.
- There are some interesting findings that extend the results of Henrik's previous Lancet paper. It will be of interest to further break down age groups of cancers (e.g., leukemias are primarily an issue for person with Down syndrome in childhood, but not in adulthood). In addition, it would be helpful to break down leukemias into acute and chronic instead of lymphoid, myeloid and monocytoid. There are interesting differences by sex. In this analysis, we'll be able to look at different types of Down syndrome (by karyotype), which was not done in the previous analysis.
- Henrik doesn't need any help with this analysis right now, but will let us know when he needs advice/assistance.

7. Our next call will be Friday, May 15, at 11 a.m. Eastern time. Poul is not able to attend, but he

will be in touch with Claus before and after the call to discuss issues.

Summary  
Down syndrome/Denmark conference call  
January 23, 2009

Participants: Claus, Jan, Henrik, Sonja, Sarah Poul, Judy, Melissa, Ann, Adolfo

1. The Divisions of Human Development and Disability and of Birth Defects and Developmental Disabilities (NCBDDD) plan to provide funds to Denmark to perform studies on spina bifida, similar to those which we've worked on with Down syndrome. For that reason, Sarah, Judy, Melissa, and Ann joined us today to listen in our discussion.
2. Claus reviewed the tables that he had put together – comments on the tables were as follows:
  - a. For all tables, it will be important to look at cases with standard trisomy 21 and translocation separate from those with mosaicism. Depending on the number of cases, in some tables, the analysis will be limited to non-mosaics (exclude mosaics); in other tables, there should be three categories (standard trisomy 21, translocation Down syndrome, and mosaic Down syndrome).
  - b. For Table 4, it would be helpful to add confidence intervals.
  - c. Much discussion focused on tables looking at congenital heart defects. This information is currently available from the Medical Birth Register beginning in January 1997 – Claus told us that more data from earlier years may be available next week. Even after PDA (Q25.0) was removed (only taking away 6 cases who only had that CHD code), the frequency of congenital heart defects among persons with Down syndrome appears higher than is usually cited, making it likely that some “minor” congenital heart defects are currently included (e.g., patent foramen ovale).
  - d. For Table 8, it would be helpful if Claus could provide us with additional breakdown of the ICD10 categories for any category with  $\geq 10$  cases with Down syndrome.
  - e. We discussed the utility of medical record review of cases with congenital heart defects. For this analysis, we agreed that this was not necessary, although may be helpful for future analyses that focus specifically on heart defects among persons with Down syndrome. For analysis of hospitalizations, it may be helpful to divide up cases into three categories – (1) no congenital heart defects, (2) atrioventricular septal defect (Q21.2), and (3) other heart defects.
  - f. Table 9 shows that a number of persons with Down syndrome have more than one heart defect. It would be helpful to look at the more common combinations for persons with  $\geq 2$  congenital heart defect codes.
  - g. For Table 10, there are a large number of cases under the ICD10 code “Factors influencing health status and contact with health services” – it would be helpful if Claus could figure out what this means.

- h. For Table 10 (and other tables comparing hospitalizations among persons +/- CHD and case and controls), we need the number expressed as a rate ratio of hospitalizations by time at risk (person-year).
  - i. For Table 11, Claus only counted hospitalization for the same reason for the same person once. If a child was admitted twice for a neoplasm, this would be counted once.
  - j. We had a discussion as to whether controls should be limited to those that match to non-mosaic trisomy 21. Our original request for controls was 20 controls, matched by birth year to the Down syndrome cohort (which includes mosaics and non-mosaics), but our tables will now focus on non-mosaics. We decided that the number of mosaics is small and that this is unlikely to have an impact on our analyses.
  - k. Tables 13 and beyond currently include a pvalue, but since these tables will include a rate ratio of hospitalizations per person-year, the test of significance on these tables will be 95% confidence intervals, not p values.
  - l. Tables 20-26 are for only mosaic trisomy 21. The sense is that the numbers in these tables are too small for a separate analysis and that we should focus our attentions for now on non-mosaic trisomy 21 for this paper.
3. Sonja has put together an introduction for the mosaicism survival paper and for the hospitalizations paper. She had several questions/comments about the mosaicism paper:
- a. Given that some studies have suggested that mosaicism is more often identified in older persons, it would be helpful to look at cases for which cytogenetic analyses were performed in the first year of life. Since information on age at karyotype is available, Claus will look at median age at cytogenetic diagnosis and distribution of age at cytogenetic diagnosis for three categories of Down syndrome (standard trisomy 21, translocations, and mosaic trisomy 21) born after 1968 – he will send this to the group before the next conference call and we will make a decision by e-mail regarding how to deal with this.
  - b. Another question was whether we had information on the % of trisomy 21 cells for those with Down syndrome mosaicism. Claus checked and this information was available only on 24 of 113 cases.
  - c. Another question was whether we know the source of the sample – blood, skin or amniotic fluid. Henrik said he thought all information on mosaics was based on blood, but we'll need to check to be sure.
4. We discussed plans for writing the remainder of the paper. Claus, Poul and Henrik will take the lead on putting together the Methods and Results of the papers. Sonja will work on the Discussion, once the Results are more finalized.
5. Our next conference call will be Friday, February 13, at 11 a.m. Eastern time.

Summary of Down syndrome/Denmark conference call  
December 8, 2008

Participants: Claus Svaerke, Sonja Rasmussen, Poul Thorsen, Adolfo Correa, Jan Friedman, Diana Schendel, Henrik Hasle

Claus presented a number of tables for our review. Some comments on the Tables included:

1. Table 2:
  - a. It is unclear why the numbers of cases/controls with missing birth weight and gestational age are so large. These data may only be available from the Medical Birth Register, which may contribute to this issue. Claus will check on missing data.
  - b. It was requested that Claus add a category of "missing" on the table. It was also suggested that the birth weight category of  $\geq 2500$  g be split up into 2500-3999 g and  $\geq 4000$  g.
  - c. Claus will also look at these data by birth cohort to see if it's apparent when the missing data begin.
2. Table 3:
  - a. It was requested that the columns "case" and "control" be switched since the time ratio is control/case.
3. Table 4:
  - a. It would be helpful to add confidence intervals to the incidence rate ratios on this table.
4. Table 5:
  - a. Information on CHD is from the Medical Birth Register – is this information updated at a later time? Claus will check.
  - b. Claus is waiting for a colleague to get data from  $< 1997$  from the National Hospital Register.
5. Table 6:
  - a. The rate of CHDs looks higher than is typically reported among infants with Down syndrome. Could the CHD category be including defects that are typically considered to be "minor" – e.g., patent ductus arteriosus and patent foramen ovale? Claus will send Sonja more information on the codes used for "CHD" to see if she can help with this.
6. Table 7:
  - a. Instead of total hospitalizations, it would be interesting to see the number of hospitalizations per child.
  - b. For these tables, it would be helpful for us to focus on categories with larger numbers – perhaps the top 10 or 15 causes of hospitalizations. We also can delete certain categories, such as "Down syndrome" and "Codes for special purposes".
  - c. We need to understand what the code "Factors influencing health status and contact with health services" is, since the number here are large.

7. Table 8:
  - a. Same comment as in Table 6 -- the rate of CHDs looks higher than is typically reported among infants with Down syndrome. Could the CHD category be including defects that are typically considered to be "minor" -- e.g., patent ductus arteriosus and patent foramen ovale? Claus will send Sonja more information on the codes used for "CHD" to see if she can help with this. We may want to look at more specific heart defect categories (for example, it might be helpful to look specifically at atrioventricular septal defects, also known as AV canals).
8. Table 9-15:
  - a. For the categories with large numbers of hospitalizations, it would be helpful to see the top three subcategories within those categories (for example, for diseases of the respiratory system, what is included there -- asthma, pneumonia, etc.).
  - b. In this table, it would be interesting to look at rate of hospitalizations per child for cases and controls for each category -- then look at incidence rate ratio and confidence intervals.
  - c. Claus is still working on "Days in bed 94-" and "Nr of days at hospital according to admission and discharge date" -- we will discuss more on a future call. Right now, a range is listed, rather than an interquartile range, but the eventual plan is to include IQR.
9. The hospitalizations analysis should focus on non-mosaic Down syndrome (or if numbers are sufficient, we could look at mosaic and non-mosaic cases separately).
10. Sonja will begin to draft an Introduction to the two papers: (1) Survival of mosaic vs. non-mosaic Down syndrome, and (2) Hospitalizations among persons with Down syndrome in Denmark.
11. Our next call will be Friday, January 16, at 11 a.m. Eastern time.

## Denmark Coop - Danish Agency for Tech, Science &amp; Innovation

Years 01-07 - GMS grant # 018305 - Through May 2007

Year 08 - 5 year award starting FY 07 - RFA 0007-001 - award # DD-00230

Determ. Of the relationship between infec. in preg. And cerebral palsy

Grant Year	Dates	Date Awarded	Proposed Activities	Fiscal Year \$	Dollars Initial Awd	Dollars Suppl.	Total \$ by Budget Per	1846	1858	1826	
								I.F. 00B Autis 00B I.F. C Dollars			
10 - Yr 03	2/1/09 - 1/31/09	1/09 - Year 03 Initial Award		FY 09	1257392		1257392	1846: 200,000 & 1858: 200,000 01F5: 75,000 & 03LQ: \$160,000 & 1892: 600,000 & 1897: 82,392	200000	200000	
09 - Yr 02	2/1/08 - 1/31/08	9/08 - Year 02 - Supplement 1		FY 08		111511		01F6: 40,000 & 027A: 6,282 & 1889: 35,000 & 1892: 30,219 1846: 350,000 & 1858: 600,000 & 03LQ: 180,063 & 1892:			
09 - Yr 02	2/1/08 - 1/31/09	2/08 - Year 02 - Initial Award		FY 08	1730053		1841574	600,000	350000	600000	
08 - Yr 01	5/1/07-1/31/08	S07 - Initial Base Award		FY 07	1054032		1064032	1846: 250,000 & 1858: 308,733 & 03LQ: 100,299 & 1892: 405,000	250000	308733	
07	02/01/05-4/30/07	2/07 - Supplement 2 (due to delay in peer review (new RFA))	(1) Registry-based studies of CP & autism, (2) Danish National Birth Cohort Study of infection in pregnancy and CP, (3) Danish National Birth Cohort Study of developmental effects in fetal alcohol exposure, (4) Danish National Birth Cohort study of autism	FY 07		478267		1846: 150,000 & 1858: 191,267 & 1892: 135,000	150000	191267	
07	02/01/05-1/31/07	08/05 - Supplement 1	Supplement for colab research: Randomized controlled trial of induced hypothermia for hypoxic-ischemic encephalopathy in term infants & cover salaries for Marlene Løvstien & Dorte Hvidtjorn	FY 05		88240		0273 (NIH): 34966 & 1858 (Div end of year): 53272		53272	
07	02/01/06-1/31/07	01/06 - Initial Award	(1) Registry-based studies of CP & autism, (2) Danish National Birth Cohort Study of infection in pregnancy and CP, (3) Danish National Birth Cohort Study of developmental effects in fetal alcohol exposure, (4) Danish National Birth Cohort study of autism	FY 06	1479535		2044042	F023: 50,000 & 1846: 500,000 & 1858: 400,000 & 1892: 529,535	500000	400000	
06	02/01/05-1/31/06	8/3/05 - Supplement 1	Supplement for lab activities for invest of genetic markers of risk for CP, (2) personnel needs for adding 300 mother-child pairs for lifestyle project, (3) compensation for increases in costs of supplies and salaries for existing staff (\$84,124 was provided for CP and autism activities) (\$34,177 was provided for the lifestyle project)	FY 05		266579		00F3: 58,000 & 1846: 228,575 0542: 52,493 & 1892: 604,915 & 01P6: 15,555 & 1858: 541,940 & 1846: 359979	228579		
06	02/01/05-1/31/06	1/26/05 - Initial Award	(1) MMR vaccine and Autism, (2) Infection in pregnancy and CP, (3) Developmental effects of fetal alcohol exposure, (4) Risk of meningitis in children with severe to profound hearing loss	FY 05	1574882		1861461		359979	541940	
05	02/01/04-1/31/05	12/2/04 - Supplement 3	(1) \$444,412 for proposed lab work with NICHD (2) \$56,545 for devaluation of US dollars versus the Danish Krone was donated (as not allowable per PGO).	FY 05		444412		0273			
05	02/01/04-1/31/05	8/13/04 - Supplement 2	Supplement for lifestyle study activities.	FY 04		134586		1892			
05	02/01/04-1/31/05	6/15/04 - Supplement 1	Supplement maternal and stress biomarkers activities.	FY 04		241762		0542			
05	02/01/04-1/31/05	12/22/03 - Initial Award	(1) Registry-based studies of CP & autism, (2) Danish National Birth Cohort Study of infection in pregnancy and CP, (3) Danish National Birth Cohort Study of developmental effects in fetal alcohol exposure, (4) Danish National Birth Cohort study of autism	FY 04	1084517		1935277	1892: 250,000 & 1858: 388,914 & 1846: 455,603	455603	388914	
04	02/01/03-1/31/04	10/20/03 - Supplement 2	Supplement \$101,143 provided due to decline of the U.S. dollar. No supporting documentation in the bio-suspect remainder of year 04 funding - 50% of base request was provided in Initial 04 award.	FY 04		101143		1892: 29,000 & 1846: 72,143	72143		
04	02/01/03-1/31/04	3/25/03 - Supplement 1	(1) MMR vaccine & autism, (2) Infection in pregnancy & CP, (3) Dev effects of fetal alcohol, (4) Lab development, (5) Morbidity associated with congenital abnormalities, (6) Rate of meningitis among children with severe to profound hearing loss	FY 03		377295		1858: 177,295 & 1892: 200,000		177295	
04	02/01/03-1/31/04	10/20/03 - Initial Award		FY 03	320000		796438	1846	320000		
03	02/01/02-1/31/03	11/4/02 - Supplement 1	Supplement for ongoing work related to CP and autism.	FY 03		92184		1899: 51,809 & 1858: 40,375		40375	
03	02/01/02-1/31/03	2/1/02 - Initial Award Pro Ann 02005	(1) Registry-based studies of CP & autism, (2) Danish National Birth Cohort Study of infection in pregnancy and CP, (3) Danish National Birth Cohort Study of developmental effects in fetal alcohol exposure	FY 02	580000		672184	2102: 100,000 & 1826: 480,000		480000	
02	01/01/01-1/31/02	9/26/01 - Supplement 1	Supplement Relationship between infection in pregnancy and CP	FY 01		122857		1810			
02	01/01/01-1/31/02	12/21/00 - Initial Award	(1) CP in relation to biomarkers, (2) autism & MMR vaccine, perinatal factors, and potential biomarkers	FY 01	87973		210870	1826		87973	
01	01/01/00-12/31/01	9/18/00 - Supplement 1	Supplement MMR vaccine - autism link	FY 00		84944		1826		84944	
01	01/01/00-12/31/01	12/23/99 - Initial Award Pro Ann 00013	(1) CP in relation to biomarkers	FY 00	220610		305554	1826		220610	
Totals						9,399,004	2,561,820	11,960,824	2,886,304	2,901,706	873,527

Name	Race	Gender	Title	Organization	Expertise	Email
John Meaney, PhD	w	M	Research Assoc Professor	University of AZ College of Medicine	autism epidemiology	<a href="mailto:jmeaney@u.arizona.edu">jmeaney@u.arizona.edu</a>
Frank DeStefano, PhD	w	M	medical epidemiologist, Immunization Safety Office	retired, CDC	autism epidemiology	
Catherine Y. Spong, MD	w	F	Branch Chief, Pregnancy & Perinatology Branch	NICHD	perinatal research	<a href="mailto:cspong@mail.nih.gov">cspong@mail.nih.gov</a>
Andrew F. Olshan, PhD	w	M	Chair, Dept of Epid	UNC Chapel Hill	epidemiology	<a href="mailto:andy_olshan@unc.edu">andy_olshan@unc.edu</a>
Russell Kirby, PhD	w	M	Professor, Department of Maternal & Child Health	Univ of Alabama, Birmingham	perinatal/DD epidemic	<a href="mailto:rkirby@uab.edu">rkirby@uab.edu</a>
Carolyn Drews-Botsch, PhD	w	F	Professor, Dept of Epid	Emory University	perinatal/DD epidemic	<a href="mailto:cdrews@sph.emory.edu">cdrews@sph.emory.edu</a>
Charlotte Druschel, PhD	w	F	Epidemiologist	NY State Department of Health	birth defects epidemic	<a href="mailto:cmd05@health.state.ny.us">cmd05@health.state.ny.us</a>
Barbara Stoll, MD	w	F	Chair, Dept of Pediatrics	Emory University	pediatrics/perinatal ep	<a href="mailto:barbara_stoll@oz.ped.emory.edu">barbara_stoll@oz.ped.emory.edu</a>

**Fulford, Teresa R. (CDC/ONDIEH/NCBDDD)**

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**From:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**Sent:** Wednesday, August 22, 2007 8:33 AM  
**To:** Yeargin-Allsopp, Marshalyn (CDC/CCHP/NCBDDD)  
**Subject:** FW: Resubmission NIH proposal

FYI - this is the email I got from Poul, re: Lifestyle project. Apparently Poul actually mentioned the proposal to JoAnn when they met in Atlanta in May (?) - so, there was prior communication.

Poul also sent me the agenda for the site visit - I see that Cindy Moore and Bradley Skarpness are also going, but not PGO. They are spending the time at a University retreat facility in Skagen (northernmost tip of Denmark) - the facility is actually an old summer "house" (mansion) of the royal family right on the coast - absolutely lovely and I am envious! Skagen is also lovely and once the scene of a colony of impressionist painters at the turn of the century and that thought it was lovely too - you'd recognize some of the paintings that came out of it. Anyway, although the agenda is pretty blank (to be filled in), it seems like a show and tell of all the projects, then a few days spent at the Lifestyle project annual meeting, including a day in the field with the psychologists. I am confident they will like what they see because I know and have worked with the investigators and know they are committed to their work, Poul included.

And yes, I am proud - just as you are when it comes to the activities of the DDB - I see no difference, or reason to feel apologetic of my pride or passion for a program I helped to shape and build. Fundamentally, I feel the same way about CADDRE and SEED, but the Denmark activities satisfy my own scientific passions rather than those shared among a caste of dozens, of often conflicting egos - and the egos are much smaller in Denmark and easier to work with. And my attachment and commitment is to all of them, not just Poul. And the barriers to getting work done are much lower.

Quite honestly, I don't see the same level of passion among many other people in NCBDDD - you, and Cathy, perhaps. Perhaps that is why other people view me with suspicion (based on what you have said, I gather that is the case) - they can't fathom what they see, so they make up stories to try and make sense of it. The strong, close collaboration, and the joys of the work products, scratch a deep itch in me, and that is a treasure - and it apparently shows!

Emotions aside, I stand objectively by the quality of work, and that's what counts in the end.

I had not intended to go on like this, but we rarely talk, plus I am aware of your own reservations about all of this. But, there it is - early morning reflections.

Diana

PS - I still think the infection/inflammation and CP/DD is an important trail, and we'll keep going down it, since it's what started it all in the beginning. It's that passion thing.

-----Original Message-----

From: Poul Thorsen [mailto:PT@SOCI.AU.DK]  
Sent: Monday, July 30, 2007 4:28 PM  
To: Schendel, Diana (CDC/CCHP/NCBDDD)  
Subject: VS: Resubmission NIH proposal

FYI !

Poul Thorsen Mobile phone: (b)(6) E-mail: pt@soci.au.dk Web:

**Gibbs Shields, Julie I. (CDC/ONDIEH/NCBDDD) (CTR)**

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**From:** Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP)  
**Sent:** Friday, January 30, 2009 9:44 AM  
**To:** Anne Christiansen  
**Cc:** 'Poul Thorsen'; Schendel, Diana (CDC/CCHP/NCBDDD); Williams, Randolph B. (CDC/OCOO/PGO); Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP)  
**Subject:** FW: Resuming the projektactivities

Dear Anne,

Would you please contact Randolph regarding the grant number. The previous grant number is necessary to review the history or the history of this cooperative agreement. Thanks, Nassi

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**From:** Williams, Randolph B. (CDC/OCOO/PGO)  
**Sent:** Thursday, January 29, 2009 4:26 PM  
**To:** Schendel, Diana (CDC/CCHP/NCBDDD); Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP); 'pt@soci.au.dk'  
**Subject:** RE: Resuming the projektactivities

No luck on the old CoAg number...sorry.

*Randolph B. Williams*

Grants Management Specialist  
Procurement & Grants Office  
Centers for Disease Control & Prevention  
2920 Brandywine Road, MS K75  
Atlanta, Georgia 30341  
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email: RBWilliams@cdc.gov

Please tell us about your recent experiences with PGO. Federal employees and on-site contractors, visit the [PGO Customer Satisfaction Survey](#). All others, email [PGO-Comments@cdc.gov](mailto:PGO-Comments@cdc.gov). This survey is for internal CDC use only and the results will be used to improve business services. Anyone working with CDC in any capacity is invited to participate in our survey.

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**From:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**Sent:** Wednesday, January 28, 2009 9:50 AM  
**To:** Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP); 'pt@soci.au.dk'  
**Cc:** Williams, Randolph B. (CDC/OCOO/PGO)  
**Subject:** RE: Resuming the projektactivities

Hi Nassi,

What is the status of the renewal., as well as these other issues? Do you need any assistance from me? I will be out of the office on Thursday and Friday of this week, but can be reached via Blackberry and cell phone as needed.

thanks, Diana

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**From:** Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP)  
**Sent:** Tuesday, January 20, 2009 11:02 AM  
**To:** Schendel, Diana (CDC/CCHP/NCBDDD); 'pt@soci.au.dk'  
**Cc:** Williams, Randolph B. (CDC/OCOO/PGO); Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP)  
**Subject:** RE: Resuming the projektactivities

Per Soren's email, Anne Christiansen intends to follow up on this matter with Randolph B. Williams at PGO to get information on the whereabouts of these money. Additionally, last week, I put in a request to PGO to identify exactly who is handling the closing activities for the old project at PGO and have not heard anything yet.

Nassi

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**From:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**Sent:** Tuesday, January 20, 2009 10:54 AM  
**To:** Schendel, Diana (CDC/CCHP/NCBDDD); Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP); 'pt@soci.au.dk'  
**Subject:** Re: Resuming the projektactivities

Hi Nassi,

Has there been any follow-up in response to Soren's email below?

Thanks, Diana

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Sent from my BlackBerry Wireless Handheld

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**From:** Schendel, Diana (CDC/CCHP/NCBDDD)  
**To:** Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP); Poul Thorsen  
**Sent:** Thu Jan 15 07:48:02 2009  
**Subject:** RE: Resuming the projektactivities  
Hi Nassi and Poul,

We should be able to gather together the notices of awards (with the draw-down amounts if needed) to show the history. I suspect there may be some confusion over the dollar amounts listed in either the announcements or continuation letters, versus what is actually obligated in the notice of award - to an outsider it must be confusing as the amounts can shift around (as we know).

I can say that for year one, there was a sum given as supplement or extension to cover expenses in between the end of the previous budget year (Jan 2007) and until the new award was ready (May 1 2007, for a 9 month budget period to bring it back to the old Feb 1 start date) because the paperwork for the new grant was delayed for 3 months on CDC's side - that is the source of the confusion mentioned below re: year 1.

Let me know how I can help get this sorted out.

thanks,  
Diana

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**From:** Dorte Hejl [mailto:DH@FOLKESUNDHED.AU.DK]  
**Sent:** Thursday, January 15, 2009 6:00 AM  
**To:** Irannejad, Nosrat (Nassi) (CDC/CCHP/NCCDPHP); Schendel, Diana (CDC/CCHP/NCBDDD); Poul Thorsen  
**Cc:** ks@adm.au.dk; as@adm.au.dk; Inge-Marie Qvist; Søren K. Kjærgaard; Annette Bachmann  
**Subject:** VS: Resuming the projektactivities

Dear Diana, Nassi and Poul

On behalf of Søren Kjærgaard, I hereby forward his e-mail to you with the documents in question attached.

Sincerely  
Dorthe Hejl Boye  
School of Public Health  
University of Aarhus

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**Fra:** Søren K. Kjærgaard  
**Sendt:** 15. januar 2009 11:32  
**Til:** Dorthe Hejl  
**Emne:** Resuming the projektactivities

Dear Diana, Nassi and Poul

The information that CDC considers the old project (Cooperative Agreement UR3/CCU018305) as closed financially (Anne Christiansen told us so after your telephone meeting with her the 6th January 2009) was a surprise. Poul has told us, and Aarhus University actually received a copy of a letter to Knud Gundersen and Poul Thorsen signed by Randolph B. Williams in March 2008 that the 894.814\$ was still available in the project (see attached copy of letter). However, I understand that Anne Christiansen intends to follow up on this matter with Randolph B. Williams at PGO to get information on the whereabouts of these money.

That the money stream after your communication with Anne Christiansen has been resumed from Danish Agency of Research to Aarhus University has removed a major obstacle for resuming activities in the project. However, I still have some uncertainties regarding the actual funded amount for year one and year two in the 'new' project (May 2007-12 no 1U10DD000230-01), which is also suffering a substantial delay in received payments.

To our "knowledge" CDC have funded following sums:

Year 1 (May 1<sup>st</sup> 2007- January 31<sup>st</sup> 2008) : 963,733/1,463,733\* + 100,299 \$  
Year 2 (February 2008 - January 31<sup>st</sup> 2009) : 1,730,063 + 111,511 + 353,162\*\* \$

*\* Regarding the first year I am still confused regarding the funded amounts. First we got a notification (dated May 11 2007) saying 1.463,733 \$, later I got a new notification (dated May 29 2007) in which the funding was reduced by exactly 500.000\$. As I got no official explanation, I am somewhat unsure to what degree one can count on these notifications. An explanation would be very welcome!.*

*\*\*Regarding the second year I have an additional award notice at 353,162\$ which also causes confusion. I need to know the exact total award for year 2.*

In total the agency (and thereby Aarhus University) has been awarded **at least** 2,905,606\$, but we have copies of award notices for up to 3,758,768\$

At Aarhus University we have so far received 1,518,076\$ and expect very soon to receive further 756,412\$, which have been transferred to the Danish Agency of Research.

This leaves by our calculations **at least** 631,118 \$ which should be transferred to cover expenses in the project. As it in my experience can be very difficult to get clear and secure information about economics in the projects (see first paragraph and the notes) and as the University may suffer substantial losses in relation to the old project, I need to have an official information directly from CDC, about the amounts still available (for year 1 and 2) at CDC, and whether the

sum can be released in the nearest future. I guess that such information can be provided very quickly and I will, when I get satisfactory information, immediately propose the Dean that we resume activities in the project.

If you need to ask for details I can be contacted at my mobil-phone (see below).

I do hope that you understand the severity of this matter at my end of the table and why I can't take any further risks. The State Revision Board and our rectorate have strong focus on the project right now.

Sincerely

Søren Kjærgaard  
Head of School  
School of Public Health  
University of Aarhus  
Bartholins Alle 2  
8000 Århus C

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