UNIVERSITY OF TORONTO

Long Term Follow Up on Clinical Trials - Reflections

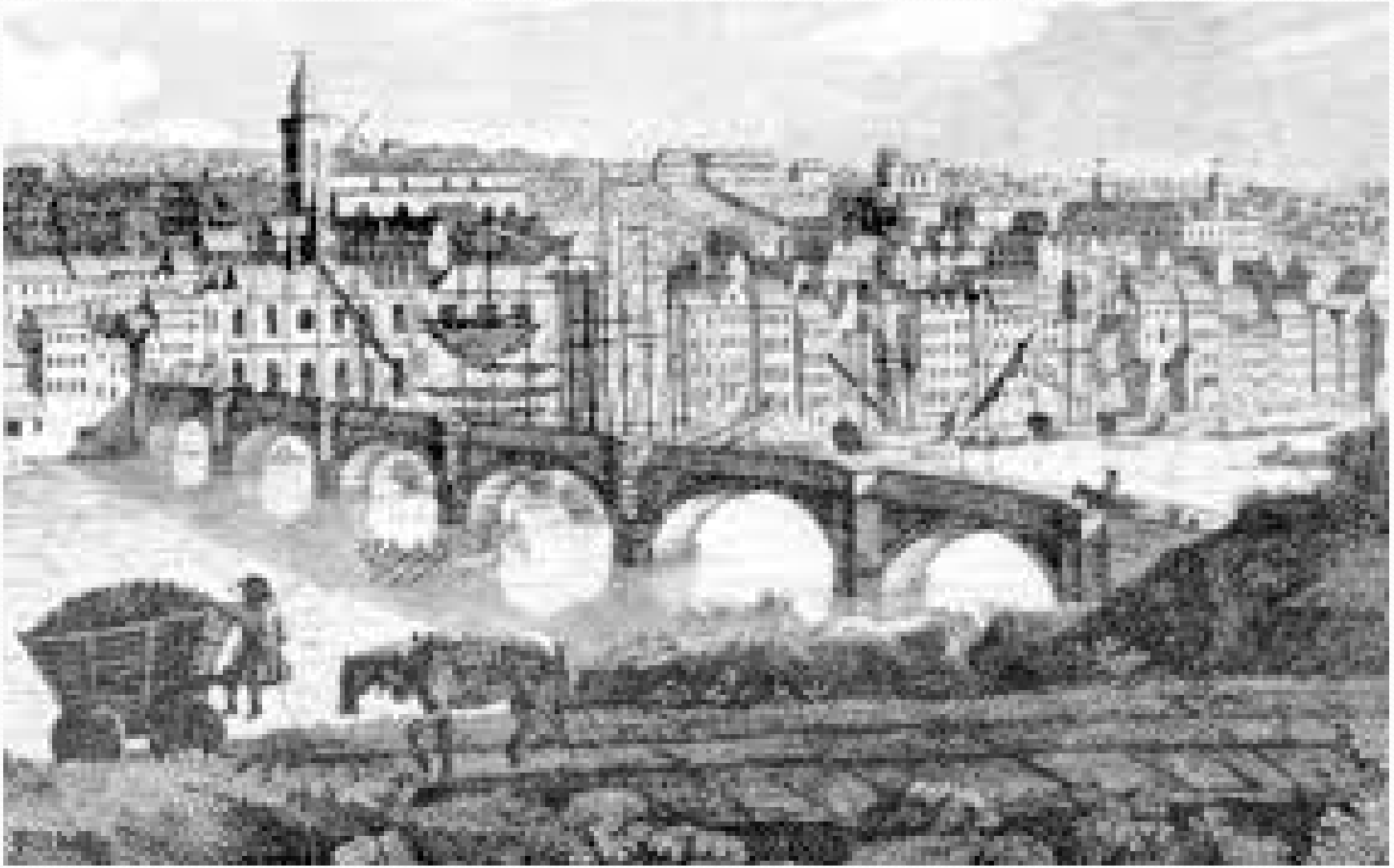
Jon Barrett MBBch, FRCSC, MD, FRCOG
Waks Research Chair in MFM
Sunnybrook Hospital

Sunnybrook HEALTH SCIENCES CENTRE

Toronto

Sunnybrook HSCS

Mmmmmm……



Mary E Hannah MSc MDCM FRCSC

- Professor, Department of Obstetrics and Gynaecology, Sunnybrook and Women's College Health Sciences
- Centre, University of Toronto
- Director, University of Toronto Maternal Infant and Reproductive Health Research Unit (MIRU) at the
- Centre for Research in Women's Health

Outline

- How to do it
- Twin Birth Study - 2 year Outcomes
  - Fetal
  - Maternal
- Reflections
  - Term Breech Trial
  - MACS
  - TBS
- Other Solutions

How to do it ?

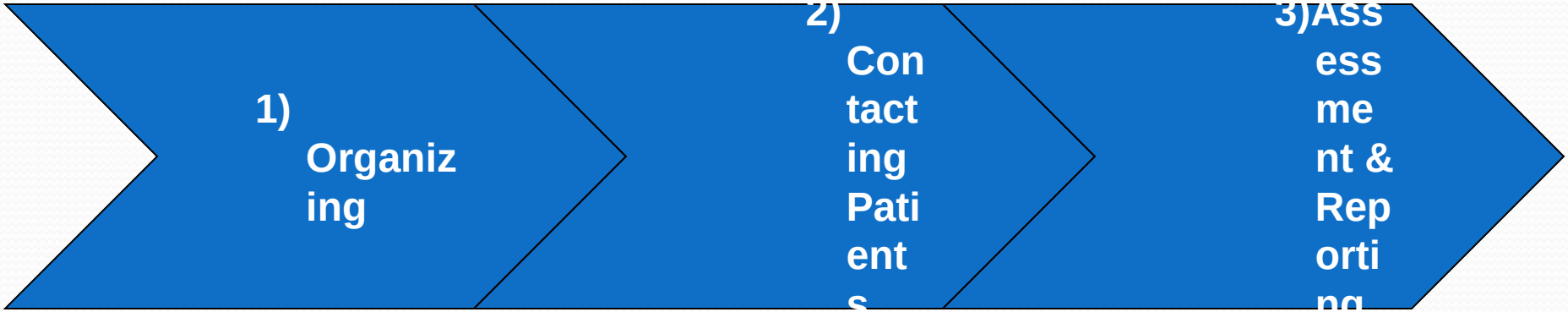
Trial Fatigue

The PI

The Centers

- Communication
  - Newsletters
  - E mails
  - Visits
- Investigator Meetings
  - Reward Excellence
  - Tips
  - New Idea
- Weekly Meetings - Up to Date

There are 3 steps to Follow-up

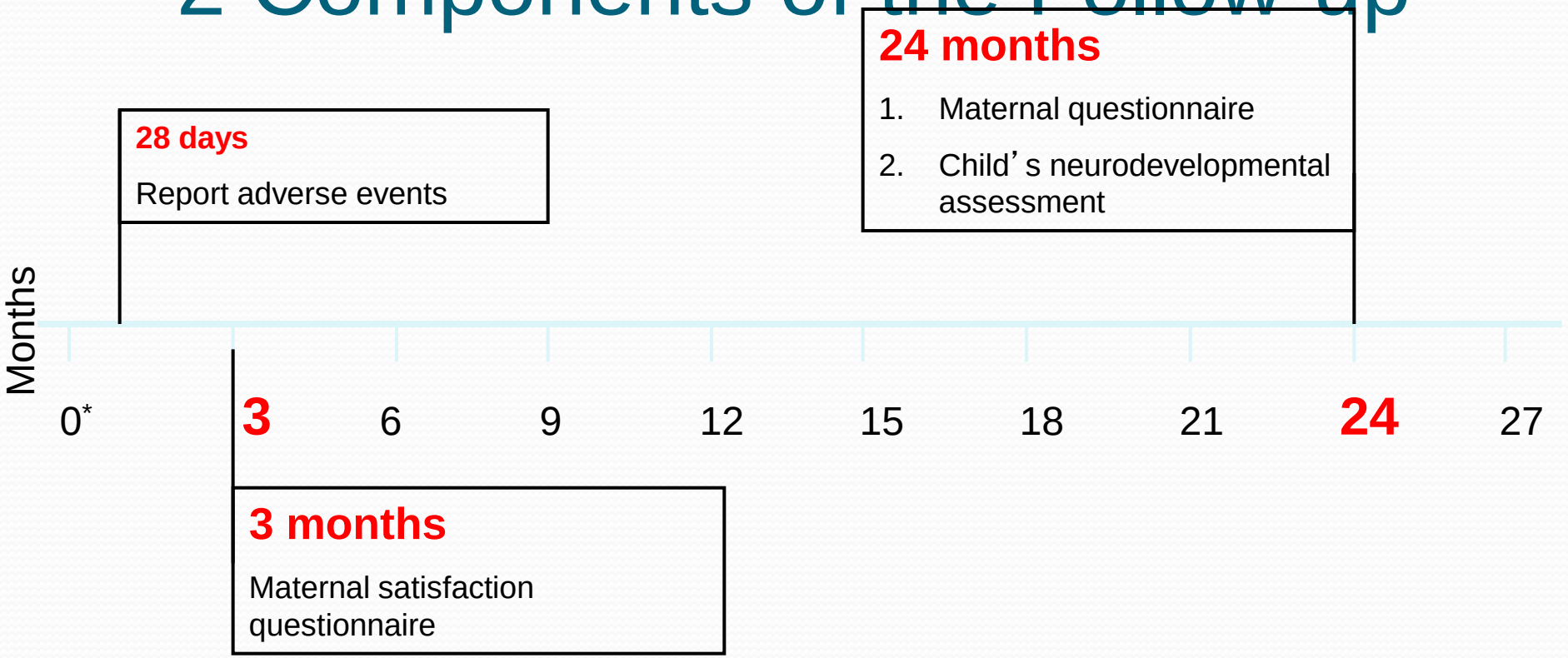


ORGANIZING

Planning for Follow-up

- What are the different components of the follow-up?
- Who is responsible?
- How will the patients be contacted?

2 Components of the Follow-up



* Note: 0 day refers to date of delivery

Who is responsible?

- Is there a plan to ensure that follow-up is conducted at your centre? Outlined on CSA
- Who will maintain contact with these families? eg. Study Coordinator
- Who will conduct the neurodevelopmental assessment? eg. Neonatologist

How will the patients be contacted?

1. 

2. 

3. 

4. 

5. 

6. 

CONTACTING PATIENTS

Overview: Contacting patients

1. Frequency of contact
2. 2 year follow-up
3. Overcoming challenges

Maintain contact every 3 months

Women who should be contacted in April 2009

6 Month Reminder

Patient Study No.	Mother's DOB	Enrolled Date	Date of Delivery
xxx-xxx-xxx	1971/05/03	2008/09/09	2008/10/20

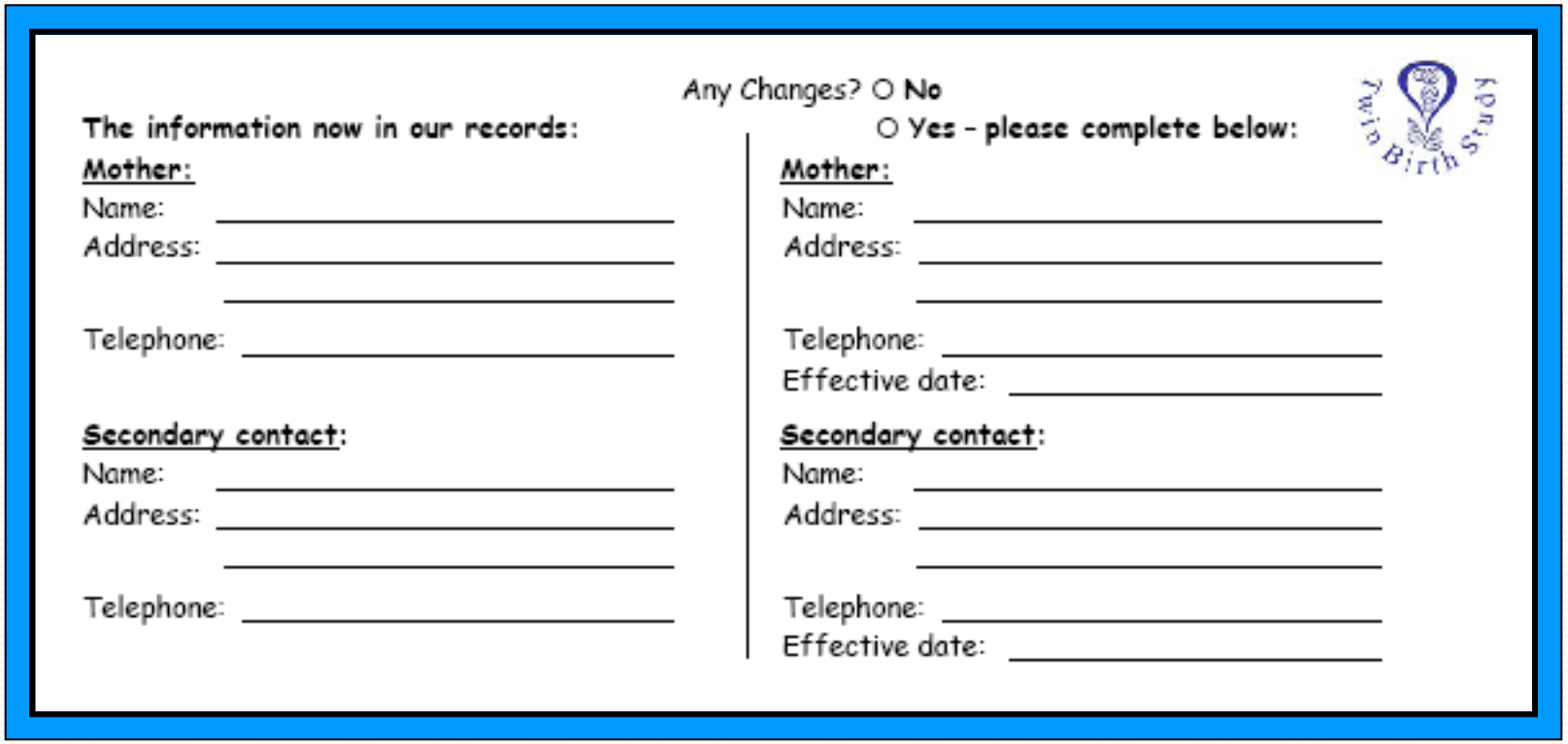
12 Month Reminder

Patient Study No.	Mother's DOB	Enrolled Date	Date of Delivery
xxx-xxx-xxx	1971/07/18	2008/03/31	2008/04/22

18 Month Reminder

Patient Study No.	Mother's DOB	Enrolled Date	Date of Delivery
xxx-xxx-xxx	1967/02/25	2007/09/11	2007/10/03
xxx-xxx-xxx	1968/07/16	2007/12/10	2008/01/17
xxx-xxx-xxx	1974/11/14	2007/12/11	2008/01/17

Send contact cards at 6 months



Any Changes? ○ No

○ Yes – please complete below:

Twin Birth Study

The information now in our records:

Mother:

Name: _____

Address: _____

_____

Telephone: _____

Secondary contact:

Name: _____

Address: _____

_____

Telephone: _____

Mother:

Name: _____

Address: _____

_____

Telephone: _____

Effective date: _____

Secondary contact:

Name: _____

Address: _____

_____

Telephone: _____

Effective date: _____

Send birthday cards at 1 year

Contact reminders for 2 year Follow-up

- Sent after 21 months
  1. 2 year maternal questionnaire
  2. ASQ window for children approaching 23-25 months gestational age
  3. Thank you cards

5 Follow-up challenges

1. Patient delivered in another hospital
2. Unable to make contact
3. Mobile population
4. Children in guardian care
5. Family lives too far from clinic

1. Patients delivered in another hospital

Strategies to connect with patients lost after recruitment

- All randomised patients are part of the study
- Ask for consent for release of information
- Continue to contact for 2 years

2. Unable to make contact

Strategies to connect with unresponsive families

- Registered letter
- Contact next of kin

3. Mobile population

Strategies to find families who have relocated

- Obtain all patient contact information
- Contact next of kin
- Use tracking services

4. Children in guardian care

Strategies to contact children in guardian care

- Contact guardian to complete ASQ
- Send mother 2 year follow-up questionnaire

5. Family lives too far from clinic

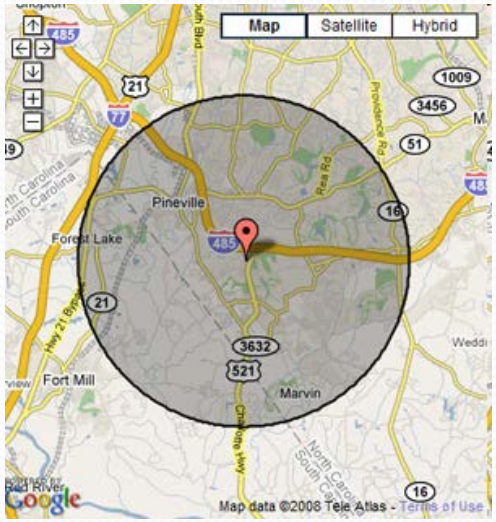
Strategies to overcome distance

- Arrange a home visit
- Contact the children's paediatrician to complete neurodevelopmental assessment by telephone

Mission accomplished!

Take Home Message

Patients were thought to be lost at the 3 month mark but were located for the 2 year follow-up after much persistence!



Keep trying!

We are here to help!

Consult the DCC with any difficulties locating the families.

Reflections

Dangerous

Difficult

Expensive

Canadian Trials Dissected

- TWIN BIRTH STUDY
- TERM BREECH TRIAL
- MACS

Sunnybrook
HEALTH SCIENCES CENTRE

The Twin Birth Study
A Randomized Trial of Planned Cesarean or Vaginal Delivery for Twin Pregnancy

Jon FR Barrett, MBBch, MD, FRCOG FRCSC
on behalf of
Mary E Hannah, Eileen Hutton, Andrew R Willan, Alexander Allen, B Anthony Armson, Amiram Gafni, KS Joseph, Dalah Mason, Arne Ohlsson, Susan Ross, J Johanna Sanchez and Elizabeth V Asztalos for the Twin Birth Study Collaborative Group*

Twin Birth Study

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

VELUT ARBOR ÆVO

Twin Birth Study (TBS)

- Initial study:
  - International, multi-center
  - Compared planned vaginal birth to planned cesarean delivery in twin pregnancies between 32 and 38 weeks gestation
  - First twin was cephalic presentation at time of randomization
  - Randomization took place from December 13, 2003 and April 4, 2011
  - 2804 women were randomized

Twin Birth Study (TBS)

- Primary research question for the initial study:
  - For twins between 32 and 38 weeks with the first twin presenting vertex, does planned CS reduce or increase the risk of perinatal/neonatal mortality or serious neonatal morbidity compared to planned VB?

Twin Birth Study (TBS)

- Sample size and analysis:
  - Total of 2800 (1400/group): 80% power, 2 - sided α error = 0.05
    - Reduction in risk of perinatal/neonatal mortality or serious neonatal morbidity from 4% (.04) with planned VB to 2% (.02) with planned CS
  - Interim analyses at 1000 and 1800
  - Final analysis
    - intention to treat
    - Generalized estimating equations (a baby will be the unit of analysis; pregnancy will be treated as a cluster)
    - $p < 0.05$ for primary outcomes
    - $p < 0.01$ for other outcomes

Perinatal/Neonatal mortality or Serious neonatal morbidity

	Planned Cesarean Section N=2783 n (%)	**Planned Vaginal Birth N=2782 n (%)**
Death	24 (0.9%)	17 (0.6%)
Serious Neonatal Morbidity	36 (1.3%)	35 (1.3%)
*Death or Serious Neonatal Morbidity	60 (2.2%)	52 (1.9%)

* OR 1.16, CI 0.77 -1.74, $p = 0.49$

Twin Birth Study

Twin Birth Study (TBS): 2-year follow-up

- Primary Research Question:
  - For twin pregnancies of $32^{0/7}$-$38^{6/7}$ weeks gestation, where twin A is presenting cephalic (vertex), does a policy of planned CS compared to a policy of planned VB decrease the combined risk of death or poor neurodevelopmental outcome of the children at or by 2 years of age, corrected for gestational age at birth?

Twin Birth Study (TBS): 2-year follow-up

- Primary Research Outcome:
  - death or the presence of a neurodevelopmental delay at or by 2 years of age as determined by
    - an Ages and Stages Questionnaire (ASQ) with an abnormal score followed by a clinical neurodevelopmental assessment (CNA) confirming the delay or,
    - the CNA completed in the absence of an ASQ.
  - In the CNA, neurodevelopmental delay is determined by a motor or cognitive delay >3 months (age at time of assessment to age of development determined by clinical assessment) or the presence of cerebral palsy.

Twin Birth Study (TBS): 2-year follow-up

- Sample size
  - Assumed a 20% lost to follow-up → **17% (83% follow-up rate)**
  - Total of 2200 clusters of twins(2200 children/group): 80% power, 2 - sided α error = 0.05 →**4603 children**
    - Reduction in risk of abnormal neurodevelopmental outcome from 2% with planned VB to 0.5% with planned CS

Twin Birth Study (TBS): 2-year follow-up

	Planned Cesarean Section	Planned Vaginal Birth
Total followed and included in analysis	2320	2283

83% Follow-up rate

Twin Birth Study (TBS): 2-year follow-up

	Planned Cesarean Section n/N (%)	**Planned Vaginal Birth** n/N (%)	**Odds Ratio** [95% CI]	**Level of Significance**	***P*-value**
Composite outcome* (death or neurodevelopmental delay at 2 years of age)	139/2320 (5.99%)	133/2283 (5.83%)	1.042	0.771, 1.409	0.79

* *Adjusted for Parity, Gestational age @randomization*

Twin Birth Study (TBS): 2-year follow-up

Variable of Interest	Levels	Odds Ratio	Conf. Limits	*P*-value*
Parity	0	0.995	0.605, 1.638	0.82
	>= 1	1.072	0.735, 1.565	
Gestational age at randomization	32^0 - 33^6	0.981	0.606, 1.589	0.87
	34^0 - 36^6	1.135	0.733, 1.758	
	37^0 - 38^6	0.926	0.407, 2.106	
Mother's age	<30	1.284	0.838, 1.967	0.16
	>= 30	0.830	0.538, 1.281	

* *P-value for testing the hypothesis that the ORs for different levels of the Variable of Interest are equal, thus providing a test for the interaction between Treatment Group and the Variable of Interest*

Twin Birth Study (TBS): 2-year follow-up

- Summary
  - We did not see a difference in the risk of death or abnormal developmental between the two groups: 5.99% vs. 5.83% (OR: 1.042, CI 0.771, 1.409) $p = 0.79$
  - The incidence of death and/or neurodevelopmental delay was higher than anticipated in the planned vaginal birth group 5.83% compared 2% assumed at the start of the study
  - No Diff in OR for > 37 weeks

We Did it – AMJOG 2016

Lets Think!

Twin Birth Study (TBS): 2-year follow-up

- Sample size
  - Assumed a 20% lost to follow-up → **17% (83% follow-up rate)**
  - Total of 2200 clusters of twins(2200 children/group): 80% power, 2 - sided α error = 0.05 →**4603 children**
    - Reduction in risk of abnormal neurodevelopmental outcome from 2% with planned VB to 0.5% with planned CS

What was the Power?

- Baseline abn ASQ 5 %
- A 50% absolute risk reduction which is unrealistic for any intervention
- 20% absolute risk reduction
- 5% to 4%would be realistic.

- 30000 patients.

Mmmmmm….

No Harm done

- No Diff Primary Outcome
- No Diff Long Term Outcome

Term Breech Trial

- *" Perinatal mortality, neonatal mortality, or serious neonatal morbidity was significantly lower for the planned caesarean section group than for the planned vaginal birth group (17 of 1039 [1·6%] vs 52 of 1039 [5·0%]; relative risk 0·33 [95% CI 0·19–0·56]; p<0·0001)." Lancet – 2002*

- *VS*

- *…the trial showed a striking difference in "serious" short-term neonatal morbidity: 0.4% versus 5.1%. SOGC 2007…… However, at two years, there was no difference in the combined perinatal death and abnormal neurological outcome…..This demonstrates the systematic failure, also shown by other studies, of short-term morbidity to predict long-term outcome in breech infants. SOGC 2007*

What was the Power?

- In Term Population Baseline abn ASQ 3%
- Reduction to 1.5% the sample size will be total 3330.
- A 50% absolute risk reduction which is unrealistic for any intervention- 20% absolute risk reduction ie 3% to 2.4% would be realistic
- 24000 patients with data. considering 20% loss of sample for ASQ- 30000 patients.

The Long Term Lie

- Breech Delivery is safe because there is no difference in long term outcome!!!

Who is being followed?

- Can only be eligible for long term outcome if survive!

The Danger of Follow up

A Positive [illegible] being out weighed by [illegible] powered Lo[illegible]ne

MACS Trial

- *" Infants exposed to multiple courses of antenatal corticosteroids had similar morbidity and mortality to those exposed to placebo (150 [12.9%] vs 143 [12.5%])." Lancet 2008*
- *There was no significant difference between the groups in the risk of death or neurodevelopmental disability: 217 of 871 children (24.9%) in the multiple-courses group vs 210 of 848 children (24.8%) in the single-course group (odds ratio, 1.02 [95% CI, 0.81 to 1.29]; P = .84). JAMA 2013*

What was the Power??

- *…. decreased weight, length, and head circumference at birth*

- *increased risk of neurosensory deafness in those who went to Term and given 1 course steroids (MACS 5)*

Is this the best way for long term Follow up??

Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease (Review)

Crowther CA, Harding JE

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

http://www.thecochranelibrary.com

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Or is this ??

- *Within two months after publication of the Term Breech Trial, the overall caesarean rate increased from 50% to 80% and has remained stable thereafter. In the group of infants < or =4000 g, this was associated with a significant decrease of perinatal mortality from 0.35% to 0.18%, a decrease of the incidence of a 5-minute Apgar score <7 from 2.4% to 1.1% and a decrease of birth trauma from 0.29% to 0.08%.*
- *Rittberg 2005, Flemix 2014*

OR This ?? - BORN Ontario

The best possible beginnings for lifelong health

833,970

Babies in the BORN Information System
(as of Feb, 2016)

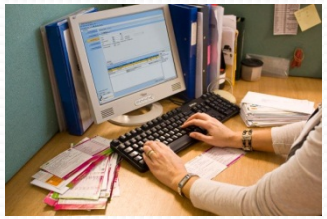
Data Centre – Where the BIS lives

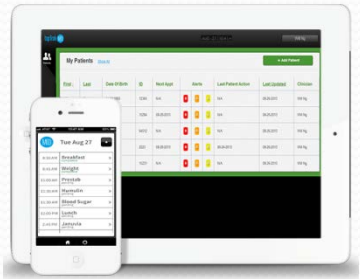
BORN Inform ata In' Process

Automatic linking and matching regardless of order of entry

BIS System

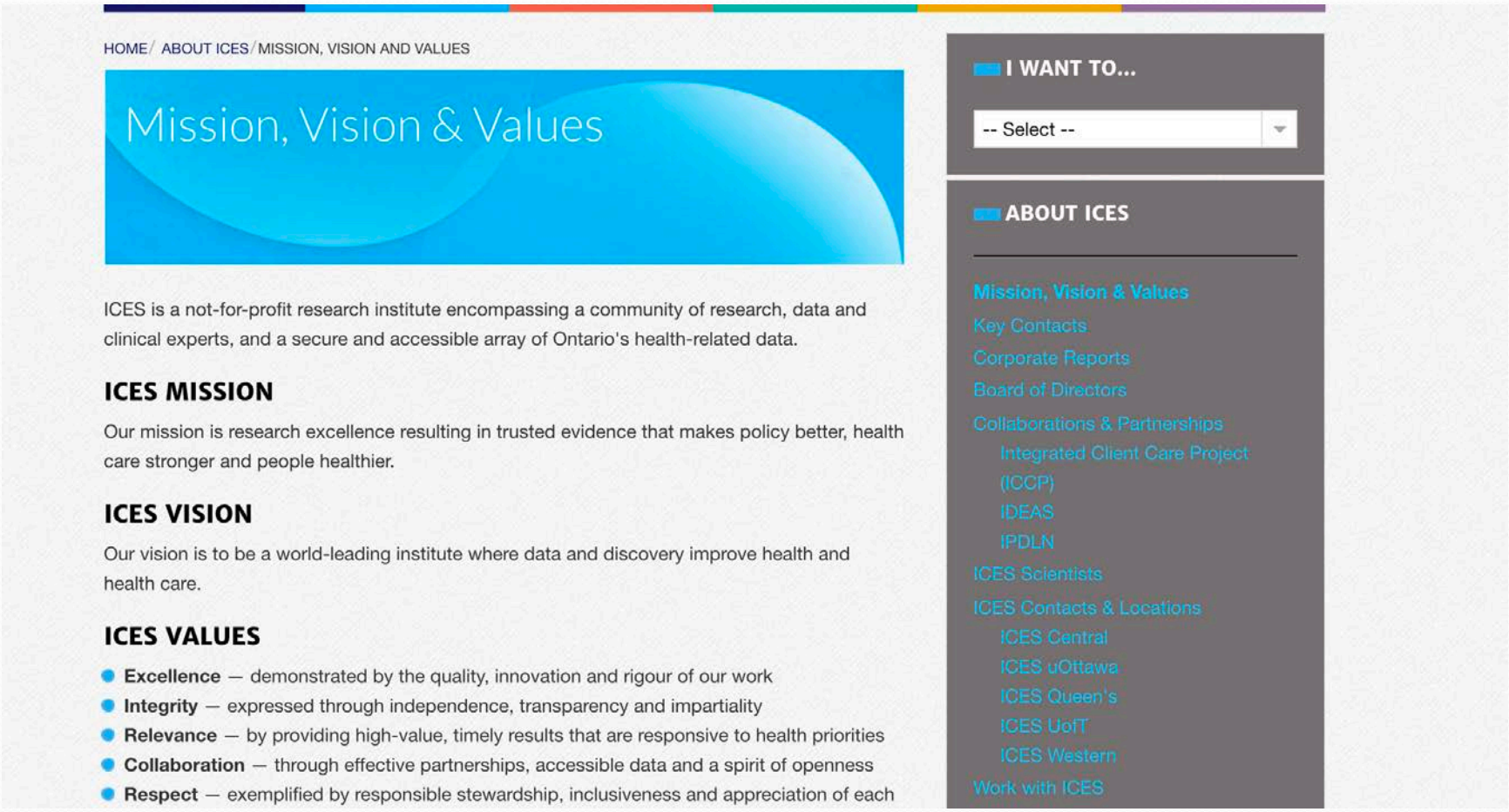
- Cycles from all IVF clinics
- Births from all 97 birthing hospitals in Ontario
- Births from all 84 midwifery practice groups in Ontario + 2 BC's
- All prenatal screening results from 5 labs (soon adding NIPT)
- All newborn screening results from NSO
- All Level 2 NICU stays - 50% of Level 3
- Prenatal and Newborn Screening follow-up results from clinics
- Primary Care: 8 FHTs provide OAR, 18 mo. EWBV





born

ICES | Institute for Clinical Evaluative Sciences



HOME / ABOUT ICES / MISSION, VISION AND VALUES

Mission, Vision & Values

ICES is a not-for-profit research institute encompassing a community of research, data and clinical experts, and a secure and accessible array of Ontario's health-related data.

ICES MISSION

Our mission is research excellence resulting in trusted evidence that makes policy better, health care stronger and people healthier.

ICES VISION

Our vision is to be a world-leading institute where data and discovery improve health and health care.

ICES VALUES

- **Excellence** — demonstrated by the quality, innovation and rigour of our work
- **Integrity** — expressed through independence, transparency and impartiality
- **Relevance** — by providing high-value, timely results that are responsive to health priorities
- **Collaboration** — through effective partnerships, accessible data and a spirit of openness
- **Respect** — exemplified by responsible stewardship, inclusiveness and appreciation of each

I WANT TO...

-- Select --

ABOUT ICES

Mission, Vision & Values
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Collaborations & Partnerships
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IDEAS
IPDLN
ICES Scientists
ICES Contacts & Locations
ICES Central
ICES uOttawa
ICES Queen's
ICES UofT
ICES Western
Work with ICES

The Toronto Data Base Linkage Project

833,970 Babies

ICES

The Solution

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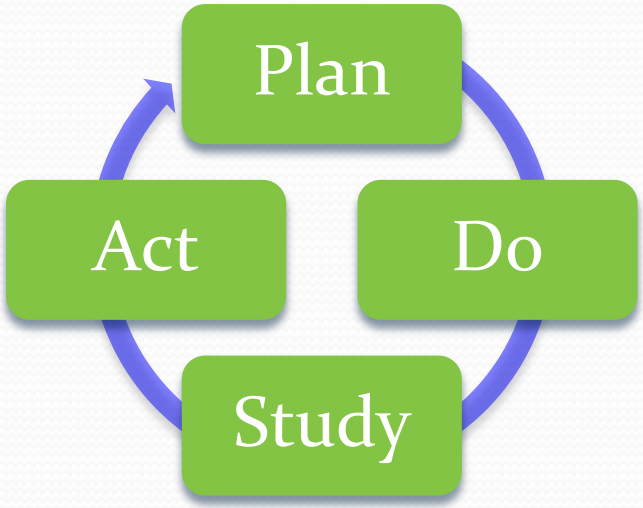
when it matters MOST

CIHR PTB Network Grant 2016

- To create a platform that will integrate into clinical practice and collect data prospectively;
- To use EPIQ (**E**vidence-based **P**ractice and **Q**uality **I**mprovement) as a tool;
- To expand an existing Neonatal national database to included Perinatal outcome that can be used to demonstrate improvement in outcomes within 5 years; and
- To build a platform that facilitates future randomized and non-randomized studies.
-

The Centre's Approach



Plan Partner with all major Centers in Canada and Provincial health and Decide Common Agenda

Do Population Intervention of what we know that works. Eg ASA,

Study 1)Link key maternal – child databases, evaluate all programs, and spread knowledge – DATA LINKAGE

2) RCT

Sunnybrook HEALTH SCIENCES CENTRE when it matters MOST

Act For Professionals and Families

THANK YOU

Sunnybrook
HEALTH SCIENCES CENTRE
when it matters MOST

MiTy Trial

Metformin in Women with Type 2 Diabetes in Pregnancy Trial

Principal Investigator: Dr. Denice Feig

Primary Question

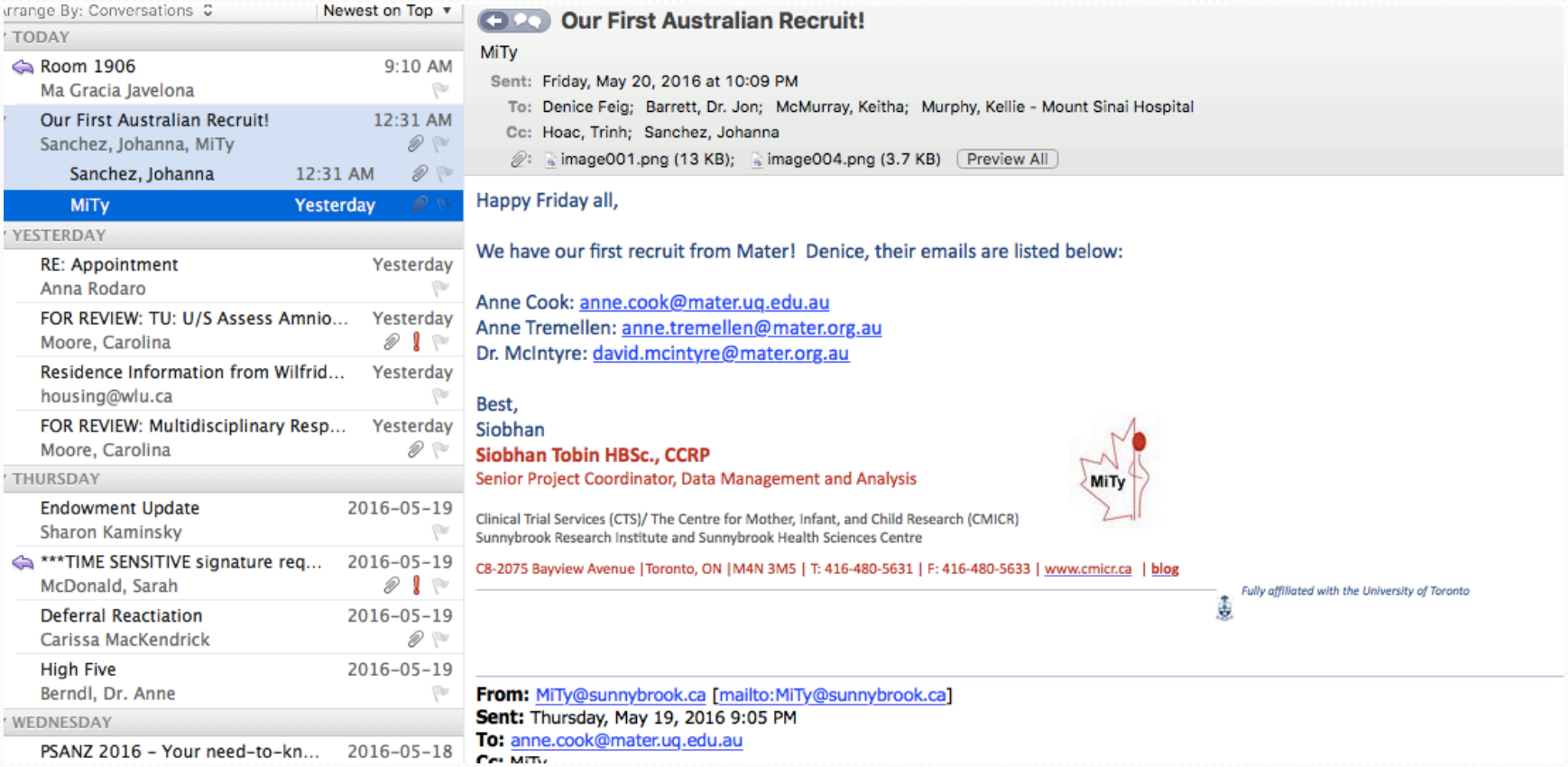
- Among pregnant women with diagnosed type 2 diabetes mellitus, does the addition of metformin to a standard regimen of insulin increase or decrease the incidence of a composite of perinatal outcomes compared with women treated with insulin plus placebo?

Study Population

- Women diagnosed with type 2 DM prior to pregnancy
- Women diagnosed with ‘undiagnosed DM’ prior to 20 weeks with HbA1c ≥6.5% (normal range up to 6%) or ≥7.0% (N range up to 6.5%)

Inclusion Criteria

- Pregnancy gestation 12 weeks 0 days - 22 weeks 6 days
- Live singleton fetus
- US done to confirm viable, singleton, no lethal anomaly
- RULE FOR GA: Based on LMP provided there is <=5 day discrepancy with US dates in first trimester and <=10 days in second trimester. If LMP dates are outside these limits, US dates will be used
- Women on metformin are included; must stop metformin prior to entering the trial; metformin use will be documented


rrange By: Conversations
Newest on Top
TODAY
Room 1906 9:10 AM
Ma Gracia Javelona
Our First Australian Recruit! 12:31 AM
Sanchez, Johanna, MiTy
Sanchez, Johanna 12:31 AM
MiTy Yesterday
YESTERDAY
RE: Appointment Yesterday
Anna Rodaro
FOR REVIEW: TU: U/S Assess Amnio... Yesterday
Moore, Carolina
Residence Information from Wilfrid... Yesterday
housing@wlu.ca
FOR REVIEW: Multidisciplinary Resp... Yesterday
Moore, Carolina
THURSDAY
Endowment Update 2016-05-19
Sharon Kaminsky
***TIME SENSITIVE signature req... 2016-05-19
McDonald, Sarah
Deferral Reactiation 2016-05-19
Carissa MacKendrick
High Five 2016-05-19
Berndl, Dr. Anne
WEDNESDAY
PSANZ 2016 - Your need-to-kn... 2016-05-18
Our First Australian Recruit!
MiTy
Sent: Friday, May 20, 2016 at 10:09 PM
To: Denice Feig; Barrett, Dr. Jon; McMurray, Keitha; Murphy, Kellie - Mount Sinai Hospital
Cc: Hoac, Trinh; Sanchez, Johanna
image001.png (13 KB); image004.png (3.7 KB) Preview All
Happy Friday all,
We have our first recruit from Mater! Denice, their emails are listed below:
Anne Cook: anne.cook@mater.uq.edu.au
Anne Tremellen: anne.tremellen@mater.org.au
Dr. McIntyre: david.mcintyre@mater.org.au
Best,
Siobhan
Siobhan Tobin HBSc., CCRP
Senior Project Coordinator, Data Management and Analysis
MiTy
Clinical Trial Services (CTS)/ The Centre for Mother, Infant, and Child Research (CMICR)
Sunnybrook Research Institute and Sunnybrook Health Sciences Centre
C8-2075 Bayview Avenue | Toronto, ON | M4N 3M5 | T: 416-480-5631 | F: 416-480-5633 | www.cmicr.ca | blog
Fully affiliated with the University of Toronto
From: MiTy@sunnybrook.ca [mailto:MiTy@sunnybrook.ca]
Sent: Thursday, May 19, 2016 9:05 PM
To: anne.cook@mater.uq.edu.au