

**TARGETING CP AS AN OUTCOME IN
NEONATAL TRIALS
HOW SHOULD THIS BE DONE?**

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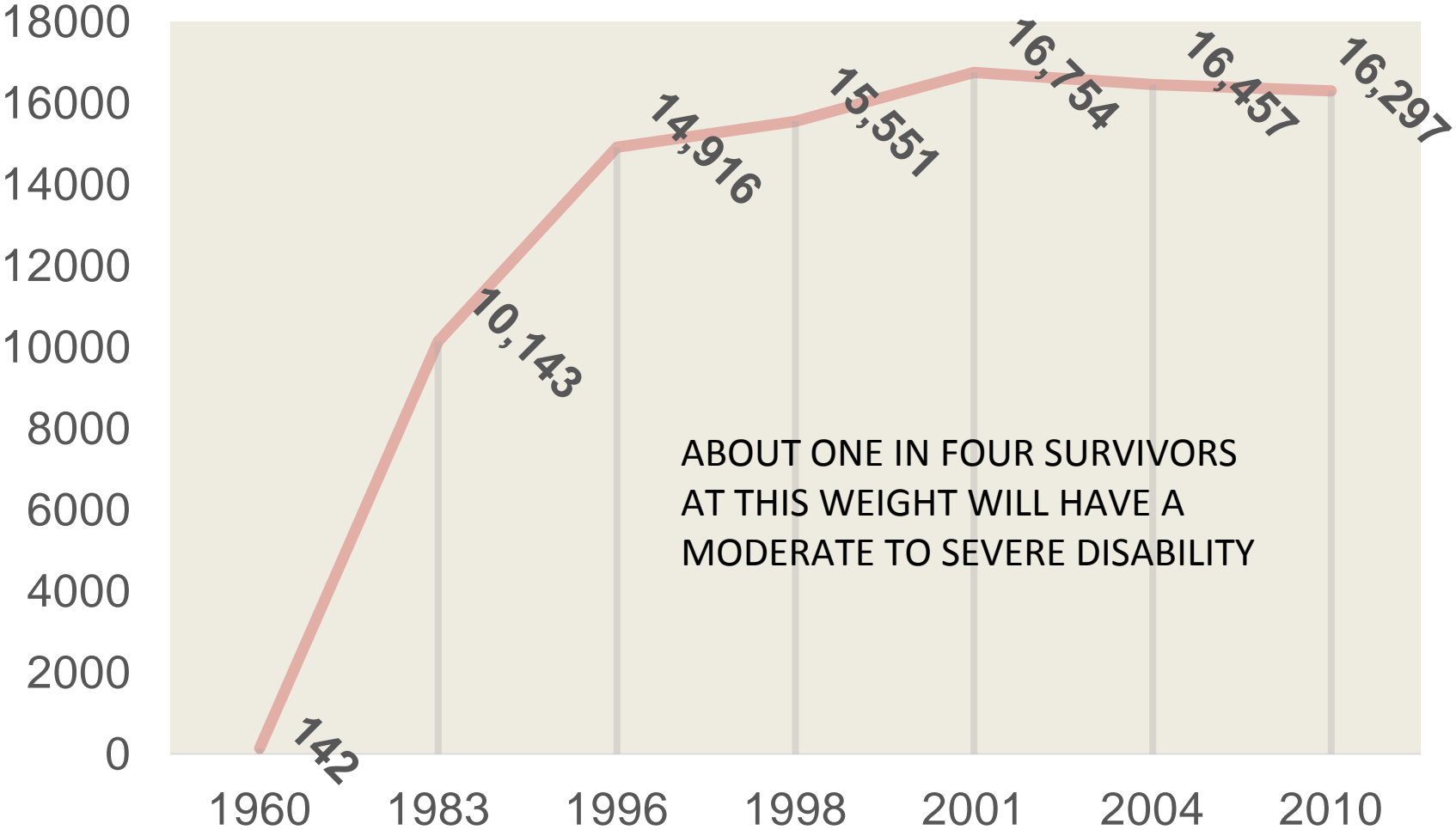
4th Biennial Michigan CP Research
meeting, Ann Arbor

March 25, 2015

ACKNOWLEDGEMENTS

Mary Gryzbowski PhD of East Carolina University and Edmund LaGamma MD of New York Medical College contributed to the development of the ideas presented here

NUMBER OF CHILDREN < 1,000 G SURVIVING TO AGE ONE IN THE US 1960-2010



ABOUT ONE IN FOUR SURVIVORS
AT THIS WEIGHT WILL HAVE A
MODERATE TO SEVERE DISABILITY

Data for 1960 based on white singletons only

THUS BETTER SURVIVAL HAS NOT MEANT LOWER RATES OF DISABILITY

- Infants at high risk of mortality are often also at high risk of later disability, such as CP.
- The 16,000 children < 1kg now surviving as a result of NIC are adding 4,000 new disabilities to the population each year
- As a result, newborn specialists have been more and more concerned about later disabilities and not just about mortality in the newborn period. Their goal is not just a survivor, but a survivor without disabilities.

TRIALS IN NEWBORNS TODAY

- We often introduce newborn treatments hoping they will reduce mortality. But we would like to know if they have an effect on later disability too. We might not want to conclude that a treatment is effective until we know that it doesn't create any later hazards, even if it saves lives in the newborn period.
- We also often think that treatments that lower mortality might also lower the risk of disability. If this is true, then adding deaths and disabilities will allow us to find a significant outcome in a trial with fewer subjects (because there are more adverse events to count)
- Finally, isn't a child free of disability the outcome we really want? So shouldn't that be the outcome of all newborn trials?

COMBINED-OUTCOME NEWBORN TRIALS

- Thus a tradition has arisen, in neonatal trials in high risk infants, that the primary trial outcome ought to be deaths and disabilities added together.
- This is statistically the same as counting the number of children surviving without disability.
- Trials with such combined outcomes must wait until the child has reached at least age two to report their findings, by which time the most severe disabilities can be assessed.

BUT FOUR PROBLEMS HAVE RESULTED FROM THIS APPROACH

1. If we use a single combined outcome, a death and a disability count the same. Is this realistic?
2. If you have an imbalance in the total number of deaths and disabilities (i.e. one outcome is much commoner than the other), noise in one outcome can obscure an important signal in the other.
3. Is it true that combined outcomes trials have more power?
4. What if you don't think that your treatment will affect mortality, just the rate of disability (e.g. CP). Are you still required to have death and disability be the outcome?

PROBLEM 1

MAKING DEATH AND DISABILITY EQUIVALENT

- Consider a trial in which death + disability is the outcome
- In arm A, there are 20 deaths and 10 children with a disability.
- In Arm B, there are 10 deaths and 20 children with a disability.
- Are the two treatments equivalent?
- In a death + disability trial, they are exactly equivalent.

PROBLEM 2

DEATH/DISABILITY IMBALANCE

- Consider a trial in which, in both arms combined, there are 100 deaths and 16 disabilities.
- In arm A there are 53 deaths and 4 disabilities
- In arm B, there are 48 deaths and 12 disabilities
- In arm A, there are 57 adverse outcomes, in arm B, 60.
 - Arm A has 10% more deaths (not statistically significant)
 - Arm B has 5% more combined adverse outcomes (not significant)
 - Arm B has three times as many disabilities (statistically significant)
 - The conclusion of the combined outcome trial is that the treatments are equivalent.

PROBLEM 3

DO COMBINED OUTCOME TRIALS HAVE MORE POWER?

- Power is only enhanced if the two outcomes are changed by the treatment in the same direction.
- But as I will show you, this depends on the kind of trial.
 - In one group of newborn trials, death and disability seem to go in the same direction and power is enhanced.
 - In another group of newborn trials, they more often go in opposite directions, making the trials more complex to analyze, and also under-powered.

PROBLEM 4

- What if your hypothesis is that your treatment will have no effect on mortality, but will reduce the risk of disability?
- Advocates of (death + disability) trials will insist that your primary outcome must include the deaths that you don't think will be altered by treatment
- If your hypothesis is correct, then a (death + disability) trial will require many more subjects and cost much more to perform.

WHAT HAVE NEWBORN TRIALS USING
DEATH AND DISABILITY AS A COMBINED
OUTCOME SHOWN?

A SYSTEMATIC REVIEW

(Grzybowski M, LaGamma E, Paneth
N, in preparation)

FIRST - THE CASE WHERE IT WORKS

TRIALS OF HYPOTHERMIA IN TERM-
BORN INFANTS WITH BIRTH
ASPHYXIA

OUTCOMES OF 7 HEAD/BODY COOLING TRIALS FOR NEONATAL ENCEPHALOPATHY (significant results bolded)

	Death RR	Disability RR In all randomized	Combined RR	Death/ Disability Ratio
Azzopardi (2005)	0.94	0.76	0.86	1.2
Gluckman (2005)	0.87	0.75	0.82	1.4
Jacobs (2011)	0.64	1.13	0.77	1.4
Shankaran (2005)	0.66	0.84	0.73	1.3
Simbruner (2010)	0.62	0.47	0.57	2.4
Zhou (2010)	0.70	0.54	0.63	1.6
Zhu (2009)	0.76	0.49	0.52	0.15
POOLED	0.75	0.73	0.74	1.27

SECOND – WHERE IT DOESN'T WORK SO WELL

TRIALS OF VARIOUS INTERVENTIONS
IN PREMATURES

NINE PERINATAL TRIALS (OF 18 WITH COMBINED OUTCOMES) IN WHICH DEATH AND DISABILITY WERE OPPOSITE

	INTERVENTION	Death RR	Disability RR	Combined RR	DEATH/ DISABILITY RATIO
Hintz (2007)	NITRIC OXIDE	1.12	0.95	1.06	2.2
INIS (2011)	IMMUNE GLOBULIN	1.04	0.97	1.00	0.87
Magpie (2006)	MAGNESIUM	1.10	0.72	1.06	9.4
Morris (2008)	PHOTOTHERAPY	1.05	0.86	0.94	0.88
Rouse (2008)	MAGNESIUM (BEAM)	1.12	0.55	0.97	3.3
Salomon (2010)	LASER FETOSCOPY	0.76	1.32	0.82	9.1
Schmidt (2001)	INDOMETHACIN	1.13	0.97	0.94	0.8
Vaucher (2012) 2 X 2 FACTORIAL TRIAL	LOWER O ₂ SAT (SUPPORT) CPAP vs SURFACTANT	1.25*	0.87	1.12	2.6
		0.83	1.16	0.93	2.6

*Lower confidence interval 1.00, p = .046

THE BEAM TRIAL OF ANTENATAL MAGNESIUM IN INFANTS < 32 WEEKS GESTATION

(Rouse et al NEJM 2008; 359(9):895-905)

- The “official” finding, i.e. the effect seen on the primary combined outcome, was null. OR for death or disability was 0.97.
- However, the abstract emphasized the “pre-specified secondary analysis” which showed a significant OR of 0.55 found for cerebral palsy in the intervention arm.
- “The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine continue to support the short-term (usually less than 48 hours) use of magnesium sulfate.....for fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery.” (ACOG Committee on Obstetric Practice and Soc Mat Fet Med: Obstet Gynec 2013; 122:727-8)
- This suggests that combined outcomes can and will be ignored in formulating clinical policy.

THE PROBLEM WE FACED

- We proposed a trial of thyroid hormone treatment in newborns < 28 weeks gestation.
- We proposed that the primary outcome be moderate to severe disability at age 3 years.
- We hypothesized no effect on death, but proposed to monitor death rates carefully.
- The primary outcome in our first application was the prevalence of disabilities in survivors. After study section argued that omitting deaths was a post-randomization exclusion, we proposed the prevalence of disabilities in all randomized infants as the primary outcome.
- We argued strongly against making death + disability/ all births as the primary outcome, which study section wanted.

PROPOSED TRIAL OF THYROID HORMONE SUPPLEMENTATION IN INFANTS < 28 WEEKS GESTATION.

HYPOTHESES: NO EFFECT ON DEATH.

30% REDUCTION IN MODERATE TO SEVERE DISABILITY

	OUR PROPOSAL		WHAT STUDY SECTION WANTED	
	TREATMENT	CONTROL	TREATMENT	CONTROL
EXPECTED N OF DISABILITIES	87	113	87 + 45	113 + 45
EXPECTED N OF DEATHS	45	45	45	45
DEATHS + DISABILITIES			132	158
PROPORTION EXPECTED WITH OUTCOME	31%	44%	47%	56%
PLANNED SAMPLE SIZE (89% POWER)	282	282	483	483
			INCREASE IN SAMPLE SIZE IS 71%	

PROBLEMS RESULTING FROM THE COMBINED APPROACH IN PERINATAL TRIALS

1. Many trials have been underpowered, because power calculations have assumed that death and disability would be in the same direction.
2. In some trials, noise in one outcome cancelled out an important signal in the other
3. The combined outcome may be ignored anyway (as in the BEAM trial).
4. A trial with a perinatal intervention in which the only hypothesis is around disability may not be performed, as was the case for our thyroid trial.

RECOMMENDATIONS FOR PERINATAL TRIAL PLANNING

- If an effect is expected on mortality, first condition the trial on death, and then consider whether follow-up is needed.
- If no effect on mortality is expected, mortality should not be incorporated into the primary outcome, but should be monitored carefully as a possible complication of treatment in the first phase of the study.
- A joint outcome should be considered only when:
 - the intervention is hypothesized to affect both death and disability
 - the hypothesized disability is severe enough to count the same as a death
 - death and disability are similar in frequency (ratio range from 0.5 – 2.0)