Assessing Risk:Benefit

Grace Montepiedra
IMPAACT Statistical and Data Management Center

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Question

- Suppose a person that you care about has just been diagnosed with MDR-TB

- Two treatment options:
  - **Regimen A:** Bangladesh regimen (9-12 months of combination of drugs containing an injectable)
  - **Regimen B:** Injectable-sparing regimen for 6 months

- Which treatment should you give?

How Do You Decide?

- Main factors
  - Efficacy (“benefit”)
  - Toxicity (“risk”)
- Other factors that might play some role
  - Duration of regimen
  - QOL measures
    - Injectables versus non-injectables

Conventional Approach: Design of Clinical Trial to Compare Regimen A vs B

- Superiority or Non-inferiority objective for efficacy outcome
- Superiority objective for safety outcome

Conventional Approach: Analysis of Outcomes

- Compare efficacy

	Regimen A	Regimen B
Treatment success rate	74%	65%

- Compare safety

	Regimen A	Regimen B
Serious adverse event rate	50%	40%

- Does the clinical benefit derived from choosing *Regimen A* outweigh the higher risk of serious adverse events?

Outline

- Risk:Benefit approach
- The IMPAACT DACS 701 experience
- IMPAACT studies with Risk:Benefit outcomes
- Benefits
- Challenges

Analysis of Patients: 4 Possible Outcomes

- Regimen A: Benefit = 74%, Toxicity = 50%

	Treatment success	Treatment failure
No SAE	47%	3%
SAE(s)	27%	23%

- Regimen B: Benefit = 65%, Toxicity = 40%

	Treatment success	Treatment failure
No SAE	28%	32%
SAE(s)	37%	3%

Risk:Benefit Outcome

- Rank the 4 possible outcomes according to *desirability of (global) outcome* in terms of patient experience

Most desirable to least desirable	Regimen A	Regimen B
Treatment success/no SAE	47%	28%
Treatment success/SAE	27%	37%
Treatment failure/no SAE	3%	32%
Treatment failure/SAE	23%	3%

- Probability that patient on *Regimen B* will have a better outcome than patient on *Regimen A* is 57% (also called the *DOOR probability*)

Risk:Benefit Outcome

- First proposed by Chuang-Stein (Statistics in Medicine, 1991)
- Follmann et al constructed ranking scheme for cardiovascular disease trials (Statistics in Medicine, 1992)
- Evans et al generalized and called it Desirability of Outcomes Ranking (DOOR) for antibiotics stewardship trials (Clinical Infectious Diseases, 2015)
- Montepiedra et al discussed in context of TB treatment trials (J Clinical Tuberculosis and Mycobact Dis, 2016)

Advantages

- “Using outcomes to analyze patients rather than use patients to analyze outcomes”
- Safety population = efficacy population
- Unified outcome that incorporates both efficacy and safety
  - study objective becomes superiority comparison with respect to this composite outcome
  - obviates use of non-inferiority design
- Can incorporate other outcomes that can figure into the risk:benefit picture (death, QOL, acceptability, etc)
- Alleviates competing risk challenges (e.g., death)
- Potential to reduce sample size

IMPAACT DACS701

- IMPAACT P1060 (Parent Trial)

LPV/r-based ART was:

  - superior to the NVP-based ART in reducing viral load (primary outcome)
  - inferior for immunologic and growth outcomes (important secondary outcomes in resource-limited settings).

- DACS701: Treatment comparisons using a patient-level Risk:Benefit outcome reflecting clinical practice*.

*To appear in Pediatric Infectious Disease Journal (Angelidou K, Palumbo P, Lindsey J et al)

Risk:Benefit Outcome

- Overall responder category:
  - Vital status
  - HIV-1 RNA
  - adverse events and changes to ART regimen
  - hospitalizations (as measure of clinically-significant morbidity)
  - weight-for-age z-score
  - CD4%
- Each component took into account:
  - status of the child after 48 weeks
  - how status had changed since starting ART
  - cross-sectional and longitudinal information
  - how a clinician would assess a child in the clinic outside the context of a clinical trial.

Consensus categorization of each of the six outcome measures used to construct the overall risk/benefit outcome

Component Outcome Measure	OUTCOME			
	Responder	**Partial Responder**	**Poor Responder**	**Non-Responder**
Vital Status Week 48	Alive	Alive	Alive	Died
HIV-1 RNA (copies/mL) (Week 48 and Longitudinal)	$RNA_{48} \leq 400$ AND no blips	$RNA_{48} \leq 400$ AND single blip <1000	$RNA_{48} \leq 400$ AND single blip 1000 – <4000	$RNA_{48} > 400$ OR $RNA_{48} \leq 400$ AND single blip ≥ 4000 OR $RNA_{48} \leq 400$ and multiple blips
Weight-for-age z-score (Week 48 and Longitudinal)	$z\text{-score}_{48} \geq -1$ AND $\Delta z\text{-score}_{48} \leq 0.5$ decline/increase	$-2 \leq z\text{-score}_{48} < -1$ at week 48 AND $\Delta z\text{-score}_{48} \leq 0.5$ decline/increase	$z\text{-score}_{48} < -2$ AND $\Delta z\text{-score}_{48} > 0.5$ increase	$\Delta z\text{-score}_{48} > 0.5$ decline OR $z\text{-score}_{48} < -2$ AND $\Delta z\text{-score}_{48} \leq 0.5$ decline/< 0.5 increase
CD4% (Week 48 and Longitudinal)	$CD4\%_{48} \geq 25\%$ AND $\Delta CD4\%_{48} \leq 5\%$ decline/any increase	$CD4\%_{48}$ 15% - <25% AND $\Delta CD4\%_{48} \leq 5\%$ decline/any increase	$CD4\%_{48} < 15\%$ AND $\Delta CD4\%_{48} \geq 5\%$ increase	$\Delta CD4\%_{48} > 5\%$ decrease OR $CD4\%_{48} < 15\%$ AND $\Delta CD4\%_{48} \leq 5\%$ decline/< 5% increase

Consensus categorization of each of the six outcome measures used to construct the overall risk/benefit outcome

Component Outcome Measure	OUTCOME			
	Responder	**Partial Responder**	**Poor Responder**	**Non-Responder**
Toxicities: Grade 3/4 signs and symptoms, laboratory values (AEs) and ARV changes due to AEs (Longitudinal)	No Grade 3/4 AEs AND no ΔARV	Grade 3/4 AEs AND no ARV dose modification/ interruption	AE that leads to a ARV dose modification/ temporary interruption	AE resulting in permanent discontinuation of ARV regimen
Hospitalizations (Longitudinal)	None	1 hospitalization with discharge ≤1 day	1 hospitalization for > 1 day	> 1 hospitalization

Results (Component Outcome Measures)

- LPV/r arm had higher percentage of "responders" for:
  - HIV-1 RNA
  - toxicity/tolerability
- LPV/r arm did as well as or better than the NVP arm for:
  - CD4%
  - Weight-for-age z-score

Composite (Overall) Outcome for DACS 701

Categories (from Best to Worst)	Description
Responder	Responder in all 6 component outcomes
Partial Responder	Not Overall (Non-Responder, Poor Responder) AND Partial Responder in ≥1 of the 6 component outcomes
Poor Responder	Not Overall Non-Responder AND Poor Responder in ≥1 of the 6 component outcomes
Non-responder	Death before Week 48 OR Non-Responder in ≥1 of the 6 component outcomes

Results for Risk:Benefit Outcome

Composite Outcome	Randomized Treatment		Cochran-Armitage trend test
Categories	NVP (N=229)	LPV/r (N=222)	p-value
Responder	28 (12%)	39 (18%)	0.002
Partial Responder	49 (21%)	66 (30%)	
Poor Responder	28 (12%)	28 (13%)	
Non-responder	124 (54%)	89 (40%)	

Primary Objectives for IMPAACT 2010 (VESTED Study)

To determine among HIV-1-infected pregnant women and their infants:

- Superiority of DTG-containing regimen versus EFV/FTC/TDF with regard to virologic efficacy at delivery

- Whether rates of the following safety outcomes differ:
  - Adverse pregnancy outcomes
  - Maternal grade 3 or higher adverse events
  - Infant grade 3 or higher adverse events

Infant Risk:Benefit Analysis (IMPAACT 2010)

The DSMB may consider the hierarchical secondary outcome to inform their decision (least desirable to most desirable)

1. Infant death
2. Spontaneous abortion (<20 weeks gestation) or fetal death (≥20 weeks gestation)
3. Infant HIV infection (Maternal VL at delivery is a surrogate for Infant HIV Infection)
4. Extremely and very early preterm (<32 completed weeks)
5. Major congenital anomaly
6. Preterm delivery (<37 completed weeks)
7. Small for gestational age (<10th percentile using WHO norms)
8. Hospitalization
9. Grade 3 or 4 adverse event
10. None of the above

Other Studies with Plans to Analyze Risk:Benefit Outcomes

- IMPAACT P1078 (immediate vs deferred INH preventive therapy in HIV-infected pregnant women): composite of mother-infant safety and TB-related outcomes
- PHOENIx (Cluster-randomized trial for TB prevention in households exposed to MDR-TB)
- SMaRT Kids (Phase III trial on MDR-TB treatment for children)

Challenges

- Developing a clear definition of the Risk:Benefit outcome is not straightforward
- When and how to design studies with Risk:Benefit outcomes as primary outcomes
- Different paradigm: requires change in the way we think about comparing interventions – can we move beyond our comfort zone?

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HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

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