Brookings-FDA Workshop

Non-Inferiority (NI) Clinical Trials: Some Key Considerations in Antibacterial Drug Studies

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Fleming TR. *Statistics in Medicine*, 27: 317-332, 2008
Fleming TR, Powers JH. *Journal of CID*, 47: 108-120, 2008
Fleming TR et al. *Clinical Trials* 8:432-439, 2011

Some Important Issues

- Many antibiotics provide
  major clinical benefit
  in settings such as Pneumonia
- Serious issue if meaningfully less effective antibiotics were used instead
- There can be differences between antibiotics in either "on target" or "off target" effects

There can be Differences between Antibiotics in either "on target" or "off target" effects

- Telithromycin in bronchitis and sinusitis
  … *liver failure & unclear efficacy*
- Daptomycin in CABP
  … *Pertel: "…not effective for Rx of CABP…"*
- Tigecycline in multiple types of infections
  … *1/3 increase in mortality rate (FDA: 9/1/10)*
- Iseganan in VAP
  … *increased trend in mortality*
- Doripenem in VAP
  … *increased pneumonia deaths*

Doripenem in VAP: …Increased Rate of Pneumonia Deaths…

7/16/08 Anti-Infective Drug Advisory Committee Meeting

	n	Mortality During IV	Pneumonia Deaths
✓ Doripenem	223	21	9
✓ Piperacillin/ Tazobactam	221	9	1
		$p = 0.03$	$p = 0.01$

Some Important Issues

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  major clinical benefit
  in settings such as Pneumonia
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⇒ **Reliable evaluation of benefit-to-risk profile of new antibiotics is necessary**

Dual Goals of Non-Inferiority Trials

- To enable a direct evaluation
  of the clinical efficacy/safety
  of **EXP** relative to **STD**

- To contribute evidence to
  the evaluation of efficacy/safety
  of **EXP** relative to **PLA**

E.g.: Doripenem (EXP) vs. Pip/Tazo (STD)

Non-Inferiority Trials… Some Requirements

ICH E9: STD should have clinical efficacy

- that is of **substantial magnitude**
- that is **precisely estimated**
- with estimates that are **relevant** to the setting in which the non-inferiority trial is being conducted

Factors invalidating Constancy Assumption
(EXP vs. STD NI Trial vs. Trials evaluating STD)

- ✓ patient characteristics

e.g., Disease caused by pathogens resistant to STD in NI Trial

- ✓ use of supportive care

e.g., Enhanced concomitant Rx attenuates effect of STD in NI Trial

- ✓ dose, schedule, level of adherence

e.g., Lower adherence to STD in NI trial

- ✓ efficacy and safety endpoints

~ well-defined & reliable *~ clinically meaningful* *~ sensitive*

Factors invalidating Constancy Assumption

✓ *use of supportive care*

7/16/08 AIDAC

DORI - 09

Doripenum	Adjunctive pseudomonal Rx: ≈ 80%
Pip / Tazo	Adjunctive anti-MRSA Rx: ≈ 15%
	45% of Dori pts received i.v. & oral therapy

…..FDA: *"The evaluation of clinical response for most patients is confounded by the prolonged use of adjunctive amikacin therapy"*

…among 109 clinically evaluable cures on Doripenem,

≥ 39 rec'd single agent Doripenem ≤ 2 days…

…FDA: *"discuss how the treatment effect of study drug will be determined in patients administered combination antibacterial therapy"*

Factors invalidating Constancy Assumption

✓ *use of supportive care*

Daptomycin vs. Ceftriaxone in CABP

Clinical Cure Rate in Clinically Evaluable Population

Pertel et al
***CID* 46: 1142-1151, 2008**

	Overall		Prior Effective Antibacterial Therapy			
			Yes		No	
	n	C.R.	n	C.R.	n	C.R.
✓ Daptomycin	369	79.4%	97	90.7%	272	75.4%
✓ Ceftriaxone	371	87.9%	92	88.0%	279	87.8%
(95% C.I.)	*(-13.8, -3.2)*		*(**-6.1**, 11.5)*		*(-18.8, **-6.0**)*	

"Daptomycin is not effective for the Rx of CAP…trials to evaluate CAP Rx may need to exclude patients who have rec'd any potentially effective prior Rx …"

Determining the **Margin** in NI Trials

Goal in NI trials: Ruling out the new intervention (EXP) is unacceptably worse than a standard (STD) regimen having *reliable* evidence of *substantial* effects…

⇒ Need an 'evidence based' NI **Margin**

Determining the NI margin: Two Key considerations

- The NI margin should be formulated using adjustments to account for bias or *inherent unreliability* in the estimate of the effect of STD in the non-inferiority trial setting. (…*as in superiority trials that are not randomized*…)
- The NI margin should be formulated to preserve an appropriate percentage of the effect of STD.

Community Acquired Pneumonia: Mortality
(Non-bacteremic patients, Age > 50)

- *Sulfonamide derivatives & penicillin. (Fleming, Powers. *CID*, 2008)

	21-day Mortality
➢ Antibiotics*	16.1%
➢ No Specific Rx	49.4%

- Consider an EXP *in patients who are candidates for Antibiotics*:

	21-day Mortality
➢ Experimental Rx	37%
➢ No Specific Rx	49%

- Is a statistically significant, but clinically modest, ↓ in mortality acceptable *in patients who are candidates for Antibiotics*?

Clinton-Gore (April 1995)

– "it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when:

1. the disease to be treated is life-threatening or capable of causing irreversible morbidity (e.g., stroke or heart attack); or
2. the disease to be treated is a contagious illness that poses serious consequences to the health of others (e.g., sexually transmitted disease)."

The Choice of the **Margin** in a NI Trial

ICH E10: "The determination of the **margin** in a non-inferiority trial is based on both *statistical reasoning* & *clinical judgment*, and should reflect uncertainties in the evidence on which the choice is based, and should be *suitably conservative*."

Some state: 'We need to streamline the scientific process to reduce the *burden* on clinical development'

Principles & Insights

"Opportunity is missed by most people because it is dressed in overalls and looks like work"

Thomas Edison

'The Good' should be the enemy of 'The Unreliable'

When considering the 'public need', we should keep in mind:
…Not simply "a choice", rather "an informed choice"…

* Emerson SS, Fleming TR. 2010; *Journal of Biopharm Statistics*

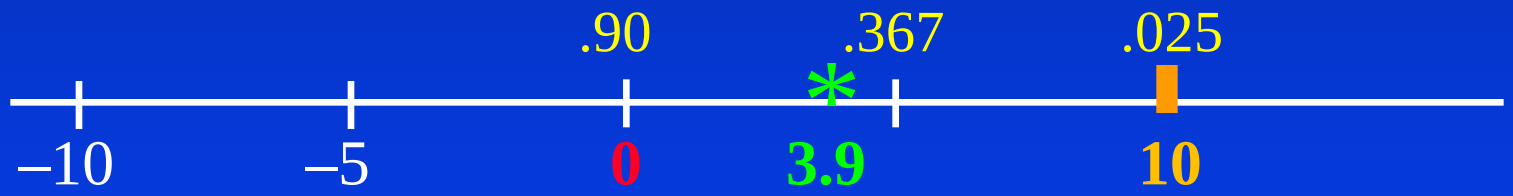
Probability of a Positive Trial

as a function of true **EXP – STD Failure Rate**

Scenario #1 (Superiority) 2N = **340** Evaluable pts

Scenario #2 (Non-Inferiority) 2N = **300** Evaluable pts

Scenario #3 (Non-Inferiority) 2N = **672** Evaluable pts



Scenario #4 (Non-Inferiority) 2N = **374** Evaluable pts