European Federation of Pharmaceutical Industries and Associations

Issues to address for a Tier C development

Aaron Dane
AstraZeneca Pharmaceuticals

Ideas in this talk

- What is Tier C and why do we need it?
- Is a smaller but Tier B-like program possible?
  - How to look across susceptible and resistant organisms?
  - How do we handle the fact that patients with resistant pathogens may have more co-morbidities?
- Interpreting information on small numbers of resistant or problem pathogens: What if Tier C is the only way?
  - Formal demonstration of superiority is not feasible
  - How do we pool information across body sites?
  - Are there areas where differing levels of data are possible?

How is Tier C Different From Tier B?

- Tier B assumes a single Phase 3 trial is feasible
  - One fully powered NI trial in an indication is possible
  - Trial probably does not enrol many MDR pathogens, but does provide randomised safety & efficacy data relevant to MDR pathogens

- Tier C is a setting where a typical Ph3 trial is not possible
  - Pathogens are uncommon, so fully powered studies not feasible
  - Aim to conduct smaller pathogen-based study(s) across body sites
  - This program uses information on the drug's activity vs. susceptible and resistant isolates to aid registration

What is a typical Tier C program?

- **Tier C:** Two small active treatment studies + one observational study
  - Prospective, randomized, open-label study of Drug C vs. BAT[2] across multiple body sites (Y1, Y2, Y3) in known (or high-risk) MDR settings. N ≅ a few hundred
  - Open-label companion salvage study of Drug C for MDR pathogens (no BAT exists)
  - Observational study of (inadvertent) ineffective therapy for the target pathogen (reference point for active therapy studies)[3]

- **Why is this pathway important?**
  - It may not be possible to develop some agents with Tier B
  - Example: A traditional NI-based HAP-VAP program for a narrow-spectrum anti-pseudomonal would require ~3000 patients[3]

[2]BAT = Best Available Therapy, standardized insofar as possible. [3]There is no easy way to provide a good control group: Ineffective therapy does not mean no therapy and also might quickly be replaced with active therapy. One might also use modern data (pharmacometric estimates of placebo response rates: AAC 56:1466, 2012), pharmacometric analyses with the new drug, or historical estimates of true placebo response rates.
[3]Assumes ~20% rate of *P. aeruginosa*, 90% power, 10% margin, 80% success rate.

Ideas in this talk

- What is Tier C and why do we need it?
- Is a smaller but Tier B-like program possible?
  - How to look across susceptible and resistant organisms?
  - How do we handle the fact that patients with resistant pathogens may have more co-morbidities?
- Interpreting information on small numbers of resistant or problem pathogens: What if Tier C is the only way?
  - Formal demonstration of superiority is not feasible
  - How do we pool information across body sites?
  - Are there areas where differing levels of data are feasible?

Is a Single Small Phase 3 RCT Possible?

- For descriptive purposes, we've said
  - Tier B: A single relatively standard design Phase 3 RCT is possible
  - Tier C: Such a P3 RCT is not possible
- But is there a step in between?
  - Standard P3 RCT is a powerful source of unbiased data
  - It addresses safety & efficacy and reduces risk for developer & regulator
  - It would be preferable to perform at least one RCT, but a smaller one
- Ideas for getting more from a smaller P3 RCT
  - Susceptible and resistant isolates
  - Different statistical criteria
  - Other ideas: More sensitive endpoints, Bayesian priors

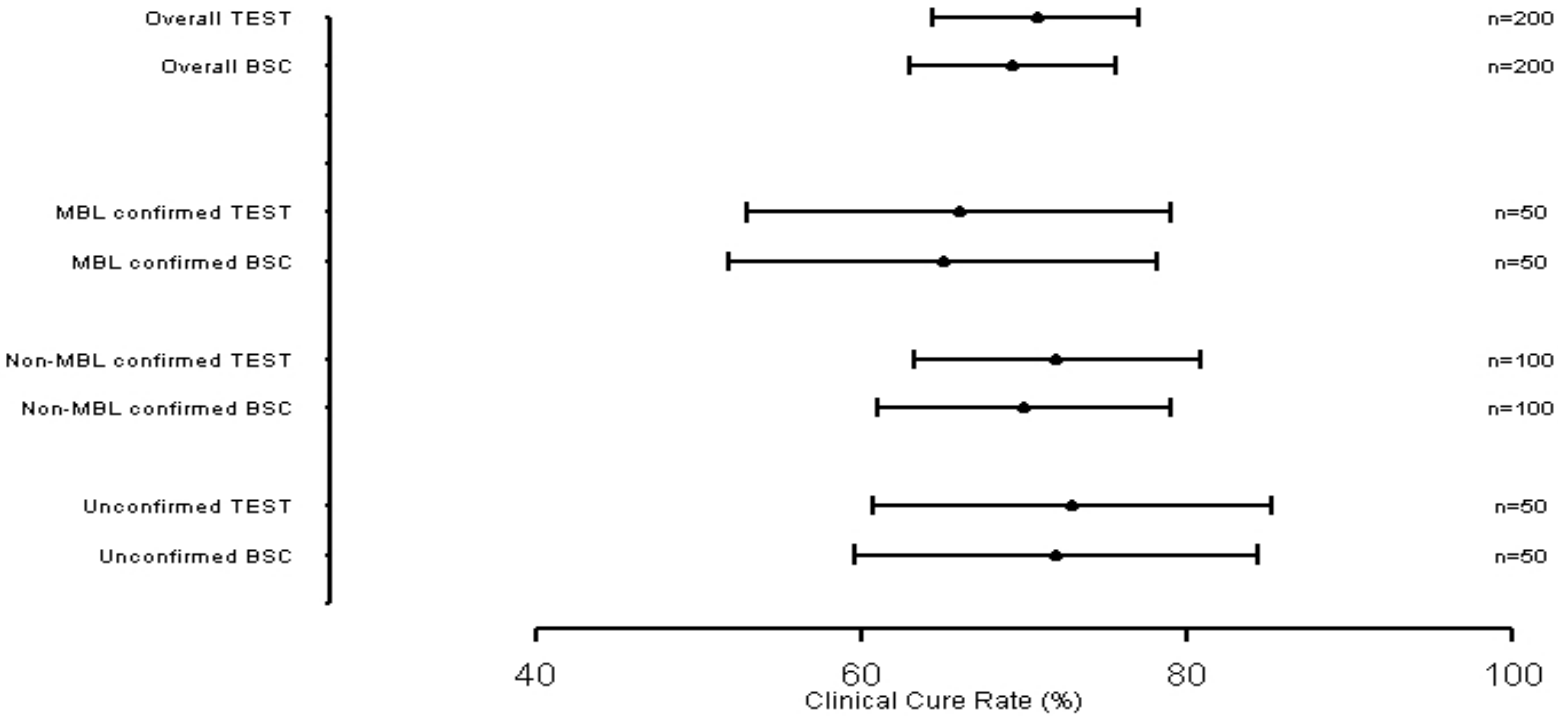
Susceptible and Resistant Isolates

- Consider results from all isolates (S & R)
  - Efficacy on susceptible isolates provides important information
    - Most reliable when R to other drugs does not affect test drug MIC
    - If MICs shift very little PK-PD link applies across MDR and non-MDR pathogens
    - Activity vs. non-MDR is relevant when assessing MDR pathogens
  - Therefore show that efficacy results on resistant pathogens are consistent with those from susceptible pathogens (response rate or treatment effect)

- This might be especially helpful when data are being provided for multiple indications
  - Sites have different response rates (cUTI is higher than HAP-VAP)
  - Both rank order and magnitude of response across indications may be helpful when analyzing small datasets

Exploring MDR and non-MDR pathogens

- Aim to show consistency for MDR and non-MDR pathogens
- Given possible co-morbidities, this could be similarity of treatment effect rather than similar response rates



Different statistical criteria

- What result will support approval?
  - For high(er) unmet need, a greater degree of uncertainty may be reasonable
- Wider NI margin?
  - There is often evidence of a big benefit over placebo from historical data
  - A wider margin with less discounting is justified in areas of unmet need
  - This will make conducting adequately powered trials more feasible
- Alternative value of alpha?
  - Traditional 2.5% alpha means we have a $\leq$2.5% chance per trial that test agent is truly worse than the pre-defined NI margin when we conclude NI
  - Applying alpha of 5% or 10% would mean only a 5% (or 10%) chance that the test agent was truly worse than the margin

Effect of changing margin & alpha

- With typical parameters (80% response, 90% power)
  - Usual alpha = 0.05 (0.025 as one-sided) and 10% margin
  - Size would be 337/arm evaluable patients

- This can be reduced 2/3rd or more
  - alpha = 0.10 (0.05 as one-sided), 10% margin → 122/arm

Evaluable patients needed/arm

1-sided alpha	NI margin		
	-10%	-15%	-20%
0.025	337/arm	150/arm	85/arm
0.05	275/arm	122/arm	69/arm
0.10	211/arm	94/arm	53/arm

Bayesian methods

Using external clinical trial data can reduce Ph3 trial size making trials more feasible

- Relies on sufficient quality & quantity of historical data
- Ability to use data depends on similarity of control response in historical data & clinical trial
  - If response rates are not similar, less ability to borrow information and becomes more like a traditional Ph3 trial
  - Will not work if we need traditional Ph3 sample size
- Can be used when we have strong belief response rates will be similar to allow confidence analysis can use historical data.

Use of more sensitive endpoints

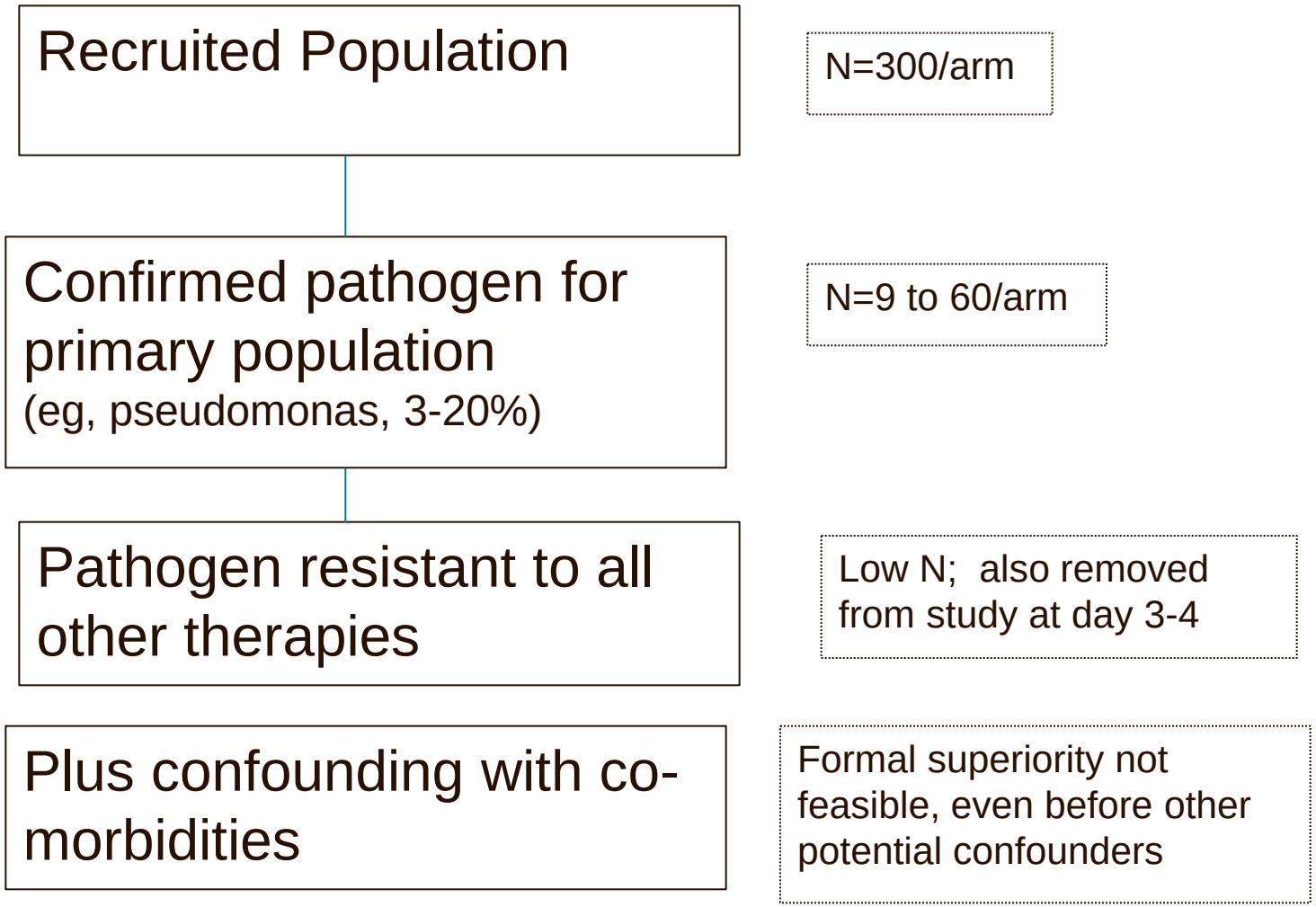
- Ordered response (mortality, failure, success)
  - Provides more detailed information than dichotomous endpoint
- More sensitive continuous endpoints
  - E.g., time to clearance, time to improvement in oxygenation, etc.
  - Must establish basis for use, particularly in NI trials, but some have a strong biologic logic

All of the approaches so far still assume it is feasible to recruit a relatively large number of patients…

Ideas in this talk

- What is Tier C and why do we need it?
- Is a smaller but Tier B-like program possible?
  - How to look across susceptible and resistant organisms?
  - How do we handle the fact that patients with resistant pathogens may have more co-morbidities?
- Interpreting information on small numbers of resistant or problem pathogens: What if Tier C is the only way?
  - Formal demonstration of superiority is not feasible
  - How do we pool information across body sites?
  - Are there areas where differing levels of data are feasible?

Why is superiority so difficult in RCT?



When only limited data are possible…

- This is real a problem
  - Gram-positive agent in HAP-VAP: Concurrent regimen for Gram-negatives will cover all but MRSA. This creates a very small micro-proven ITT group.
  - But, we still want some form of control! What are our choices?
- There would seem to be several related possibilities
  - A *very* small RCT (so small that inferential testing is not possible)
  - *Open-label* data
  - Pooling across body sites
- Use of external data for MDR pathogens
  - To be reliable and credible external control should include contemporary patients with well documented disease and endpoints
  - To assess how new drug compares with no treatment / ineffective treatment need sufficient data to assess comparability with clinical trial data

EFPIA are keen to work with EMA on methods using historical control data or developing new methods to collect contemporary, external control data

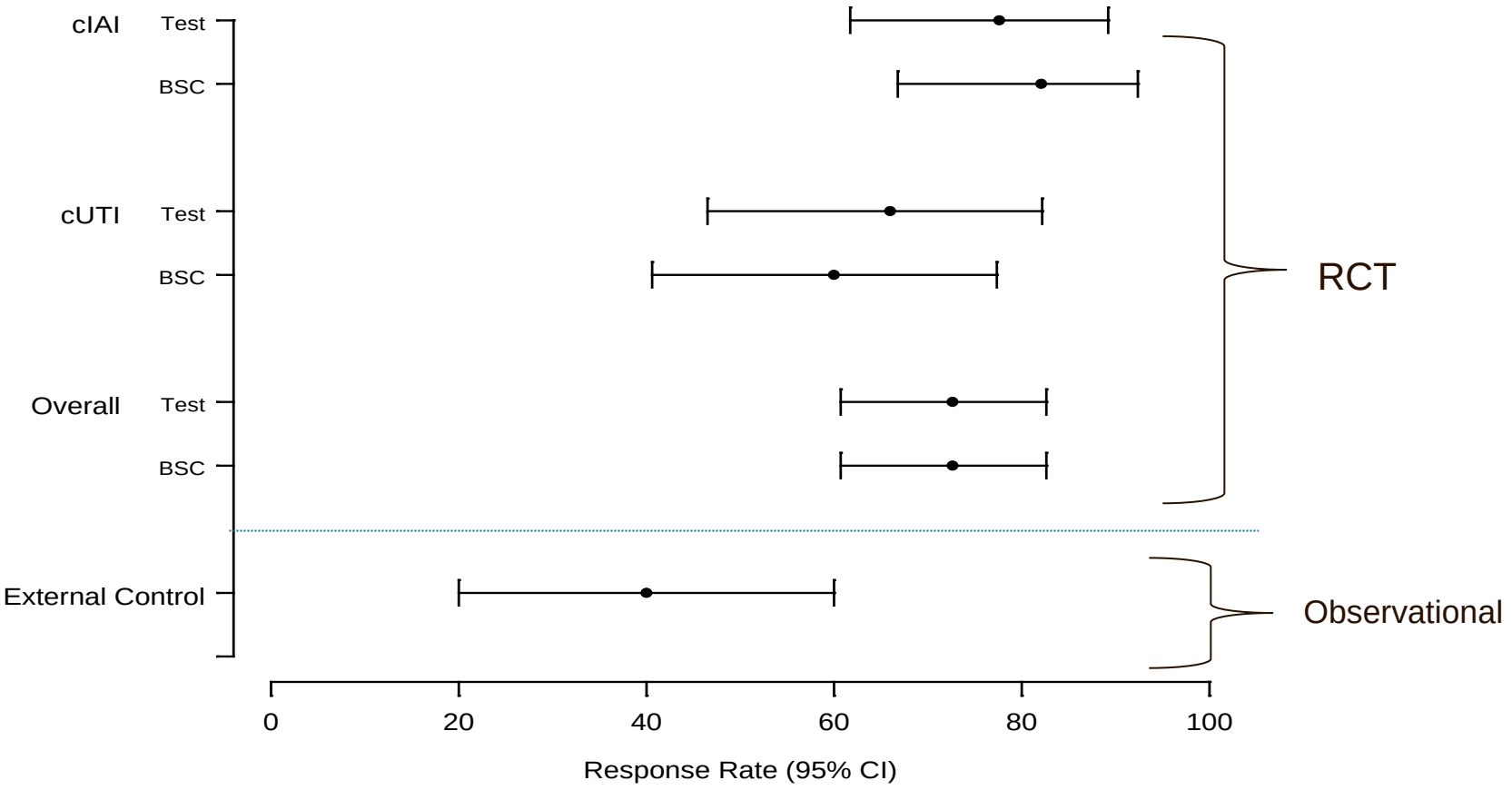
Pooling across body sites

With uncommon pathogens, it is necessary to pool across body sites

- Need a strong prior belief that pooling across stated body sites is reasonable
- Statistical methodology
  - Simple vs. weighted pooling; Bayesian information borrowing across body sites
  - Possibility of different endpoints across body sites
  - Careful use of the correct metric (Absolute or relative differences or Odds Ratio)

What result would support approval?

- For MDR pathogens where inferential testing is not feasible
  - Provides evidence of acceptable response rate & indirect benefit over inadequate therapy



Conclusion

- Traditional statistical approaches are not possible
- Consistency of susceptible and resistant pathogens should be used to interpret new agents along with evidence of benefit against resistant pathogens
- Further discussion and evaluation of statistical techniques
  - Bayesian approaches
  - Pooling across body sites
- EFPIA keen to engage in discussions and work refining statistical techniques or the use of external control data