ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Council on Antibacterial Drug Development

Meeting #1

The Brookings Institution

August 30, 2012

Report on the CTTI Statistics Think Tank for Anti-Bacterial Drug Development

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August 30, 2012
Brookings Institute

Outline

- Overview of CTTI Statistics Think Tank
- One- versus two-study paradigm
- Non-inferiority trials and alternative approaches
- Data from multiple infection (body) sites
- Prior therapy
- Data availability and new data collection

CTTI Statistics Think Tank

- Clinical Trials Transformational Initiative (CTTI) convened the Statistics Think Tank for Anti-Bacterial Drug Development on August 20, 2012 in Bethesda
- Meeting objective: *To discuss innovative approaches to the design and analysis of clinical trials in anti-bacterial drug development.*
- Discussion to focus on non-inferiority trials and include Bayesian approaches that can incorporate both historical data on active control products and mechanistic data arising from PK/PD and other pre-clinical studies

CTTI Statistics Think Tank

- Participants
  - Four biostatistics faculty members
  - Four statisticians from industry
  - Four government statisticians (external to CDER)
  - CDER statistical review team for anti-infectives
- Areas of expertise included
  - Clinical trials methodology
  - Bayesian methodology
  - Non-inferiority trial designs
  - Other (meta-analyses, missing data, hierarchical modeling)

CTTI Statistics Think Tank

- Just one of a number of initiatives FDA is undertaking to promote anti-bacterial drug development
- Provided an opportunity for leading experts in clinical trial methodologies to discuss alternative approaches to design and analysis that may prove useful for anti-bacterial programs
- Ultimate goal is to increase the likelihood that clinical trials of promising agents are successful and to ensure that those agents, if approved, are in fact safe and effective therapies for the intended patient populations

CTTI Discussion Topics

- FDA statistics review team identified four broad areas to focus the discussion
  1. One- versus two-study paradigm: When does it make sense to plan for a single, confirmatory study as sufficient evidence of efficacy and safety in treating antibacterial infections, what particular requirements should be placed on such a study, and what types of supporting evidence should be required?
  2. Non-inferiority trials: Are there more efficient ways to establish non-inferiority to an existing therapy, when placebo controlled studies are not ethical/possible, given the many challenges in this disease area?

CTTI Discussion Topics

- Discussion areas, cont.
  3. Multiple (body) sites of infection: Are there efficient ways to combine information across multiple (body) sites for a single pathogen, or across multiple pathogens for a single (body) site to better inform confirmatory trial designs and analysis?
  4. Trial logistics: Are there innovative ways to approach a variety of other problems with anti-bacterial trials, e.g., accounting for prior therapies that cannot be withheld?

Discussion Area #1

ONE STUDY PARADIGM

One-Study Paradigm

- Design issues
  - Size of study, power, and representation of subgroups
  - Representativeness of study population – more sites with fewer patients per site more attractive, given the non-sampling environment of clinical trials
- Analysis and results:
  - Level of evidence
    - Move beyond p-values and consider totality of evidence in the form of the posterior distribution of the treatment effect
  - Consistency across subgroups

One-Study Paradigm

- Replication
  - Quality is critical in non-inferiority (NI) trials; poor trial conduct can cause bias towards the alternative
  - Two successful studies designed and conducted by two groups of investigators with similar results adds confidence in this setting
  - Independence (and, therefore, replication) may be questioned, if the margin is derived from the same historical data
  - May not be ethical to conduct a 2nd trial, once results of the first are available

One-Study Paradigm

- Single study with p-value < 0.05
  - Chance of replication is 50:50➔supportive evidence needed
- Medical device analogue: Mechanism of action plus one confirmatory trial sufficient for submission
- Pharmacologic or pre-clinical data
  - In vitro 'kill' studies
  - Exposure response data from animal models
- Exposure response in humans from phase 2 studies
- Differentiate between NMEs and drugs approved for other indications

Discussion Area #2

NON-INFERIORITY TRIALS

Non-Inferiority Trials

- Ideally, have probability distribution for placebo, control, and test drug and compare the three; degree of overlap may be informative
- In addition to comparing against NI margin, point estimate and level of precision (width of confidence interval) are important
- 3-arm trial: test treatment vs. active control vs. placebo
  - Rescue offered for placebo patients (quickly)

Non-Inferiority Endpoints

- If mortality is a component of the clinical endpoint, and we know the treatment difference (M1) for mortality, can we say the difference for the clinical endpoint is at least as large?
  - E.g., 10% margin for mortality; 12.5% margin for response?
- Ordinal outcome: Mortality vs Clinical Failure vs Clinical Success
  - Proportional odds regression for analysis
  - Treatment effects in terms of odds ratios may not be ideal
- Are there studies that have data on both mortality and clinical cure that can be used as a bridge?
- *Note: Motivated by lack of data to compute margin, not sample size*

Bayesian Approach

- Bayesian approach for determining NI margins
  - Dirichlet process with meta-analysis (Tiwari, et al. 2012)
- Bayesian model for NI analysis
  - Historical data for prior on active control (Gamalo, et al., 2011)
  - Non-informative prior for test drug
  - Potential issue with bias/confounding
  - Suggestion to assume a prior on the difference between test drug and control (from early phase studies)

Bayesian Approach to NI Margins

- HABP/VABP example:
  - Estimate the drug effect relative to placebo using historical data on active control and inadequate or delayed therapy.
  - Margin computation from Sorbello, et al., 2010

HABP/VABP Data

- All-cause mortality for inadequate or delayed therapy:

Studies	ITT (N)	Therapy	All-cause Mortality, n/N (%)
[1]	130	Inadequate	31/51 (61%)
[2]	76	Delayed	33/52 (64%)

- All-cause mortality rates under active therapy:

Studies	ITT (N)	Active Control groups	All-cause Mortality, n/N (%)
[3]	124	P/T/A	27/88 (31%)
		Cef/A	8/36 (22%)
[4]	402	Cip	43/202 (21%)
		Imi	38/200 (19%)
[5]	438	Lev iv/Lev po	38/220 (17%)
		Imi iv/Cip po	32/218 (15%)
[6]	396	LZD/AZM	36/203 (18%)
		Van/AZM	49/193 (25%)
[7]	623	LZD/AZM	64/321 (20%)
		Van/AZM	61/302 (20%)

HABP/VABP Meta-Analysis

	Frequentist: DerSimonian-Laird % (95% Conf. Interval)	**Bayesian: Dirichlet Process Prior % (95% Cred. Interval)**
Inadequate or Delayed Therapy	0.62 (0.52, 0.71)	0.62 (0.53, 0.72)
Active Control	0.20 (0.18, 0.23)	0.20 (0.18, 0.21)

Frequentist (DerSimonian-Laird) treatment effect: 52%-23% = 29%

Bayesian (Dirichlet process prior) treatment effect: 53%-21% = 32%

Hypothetical Bayesian Analysis

	Study 001		Study 002	
	Experimental	Active Control	Experimental	Active Control
All-Cause Mortality	90/400	70/390	65/350	75/370
Observed Proportion	22.5%	17.9%	18.6%	20.3%
Difference (95% Conf Int)	4.6% (-1.2% to 10.3%)		-1.7% (-7.7% to 4.3%)	
Posterior Mean	22.5%	19.6%	18.6%	20.0%
Difference (95% Cred Int)	2.7% (-1.5% to 7.3%)		-1.5% (-5.9% to 2.9%)	

Historical active control all-cause mortality rate of 20%.

Bayesian Approach

- Evaluate Bayesian approach in parallel to frequentist approach and compare operating characteristics
  - Bayesian approaches also useful as sensitivity analyses, when frequentist approach is primary
- For any trial, the gain in evidence in favor of test drug depends on the strength of the prior evidence

Bayesian alpha: Probability of a true negative treatment effect when the study shows a positive effect

Prior Odds of Success#	Power = 80%	85%	90%
1.0	0.0303	0.0286	0.0270
1.3	0.0235	0.0221	0.0209
1.5	0.0204	0.0192	0.0182
1.7	0.0181	0.0170	0.0161
2.0	0.0154	0.0145	0.0137
2.5	0.0123	0.0116	0.0110

#Odds of Success based on prior information, e.g., phase 2 trials
Assume α (frequentist) = 0.025 (1-sided)
α* = Pr (H0| Reject H0) = α/(α+power*OS)

Bayesian Approach

- For a single confirmatory trial with α (frequentist) = 0.025 (1-sided):
  - Bayesian approach will result in an increased sample size requirement, unless credible prior evidence in favor of treatment exists
  - Strength of this prior evidence needs to be considered in addition to the strength of evidence from the single confirmatory trial

Bayesian Approach

- Advantages and disadvantages
  - Allows modeling uncertainty
  - May not provide efficiency—could know less than we think!
  - If historical data is not applicable to the current study, weakly informative priors can be used
  - Caution about strong assumption for exchangeability-- Patients will probably not be exchangeable across studies, but could be within a study
  - Study exchangeability assumption leads to hierarchical modeling

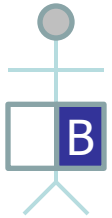
MIC-Based Approach

- Approach discussed by Dean Follmann based on recent work with Erica Brittain and John Powers.

- Related to methods of Paul Ambrose and co-authors, but attempts to:
  1. Use MIC data for superiority testing
  2. Ensure randomization protects against confounding

MIC-Based Approach

Low MIC-A Low MIC-B



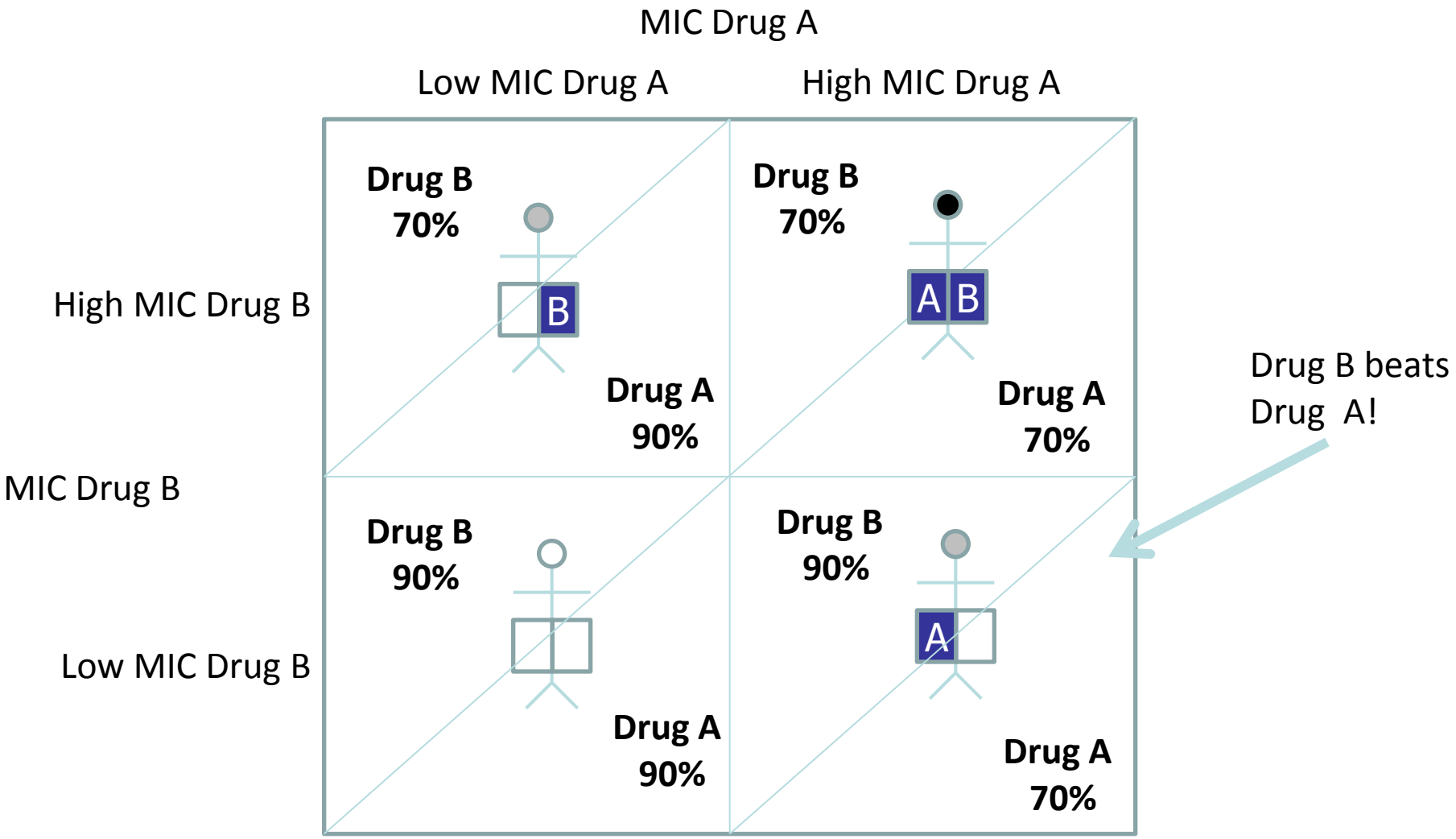
Low MIC-A High MIC-B

High MIC-A Low MIC-B**

High MIC-A High MIC-B

** Drug B should be superior to Drug A for these patients

MIC-Based Approach



MIC-Based Logistic Regression

- Logistic model regressing clinical outcome on:
  - Randomized treatment
  - Baseline MICs under both treatment and control
  - Treatment x MIC interactions

- Uses the model to test if treatment is *superior* to active control for discordant subjects whose pathogens have:
  - Low MICs under treatment
  - High MICs under control

Another MIC-Based Approach

- AUC/MIC is basically the operating dose in the blood in a patient normalized by baseline MIC
  - AUC = dose/clearance
  - The greater the AUC/MIC ratio for a patient, the greater the likelihood of successful outcome for that patient
- Idea: Conduct a randomized trial as follows:
  - Control arm -- give the fixed dose as indicated
  - Test arm -- collect PK blood levels during 2-3 days of the start of the treatment and find the ratio AUC/MIC value for that patient
  - Adjust the dose of that patient for the rest of the treatment period, so that the ratio remains in a band of suitably high values
- Compare the two randomized groups (1) for non-inferiority, and if successful (2) for superiority
- Advantage: the treated group is likely to be at least numerically superior to control

Discussion Area #3

MULTIPLE INFECTION SITES

Multiple Infection Sites

- Scenario: data are available for the same pathogen studied in several infection (body) sites, e.g., urinary tract infection, skin infection, pulmonary infection
  - Data may arise from separate studies or a single study stratified by infection site
- General agreement that simple pooling of data across sites is not appropriate
- Model-based approach preferred, e.g., hierarchical model with random effects for each infection site

Multiple Infection Sites

- Enroll patients with related infection types in a single trial, using stratified randomization
- Hypothetical example: Mortality endpoint; resistant pathogens; superiority trial

Infection types	Standard of Care	Test Drug	Difference (95% CI)
Blood stream	15/30 (50.0)	5/30 (16.7)	30.3 (9.8, 53.7)
Intra-abdominal	7/15 (46.7)	3/15 (20.0)	26.7 (-7.2, 55.4)
HAP	7/15 (46.7)	10/15 (66.7)	-20.0 (-50.7, 51.7)
Pooled	29/60 (48.3)	18/60 (30.0)	18.3 (0.9, 34.8)

Multiple Infection Sites

- Comment: One can pool results across body sites for a broader indication
  - If clinically meaningful to pool, considering disease severity and dose
  - Infection types are path-physiologically similar
  - If there is some evidence of consistency of results and replication across body sites
  - Multiplicity issues arise if claim is sought for only those indications showing positive results

Multiple Infection Sites

- In the hypothetical example
  - Results are okay for the bloodstream, e.g., p-value = 0.003 (1-sided) in favor of test drug
  - Concern: intra-abdominal infection result (p-value = 0.061, 1-sided) and HAP (wrong direction) are inconsistent with bloodstream result

Multiple Infection Sites

- Similar to the subgroup problem, e.g., treatment heterogeneity across regions in a multi-regional trial
- Bayesian approach: Assume subgroups are exchangeable in the hierarchical model; can use covariates to help
- Weigh evidence from studies of other treatments that may show similar inconsistencies across infection sites

Discussion Area #4: Trial Logistics

PRIOR THERAPY

Discussion Area #4: Trial Logistics

PRIOR THERAPY

Prior Therapy

- Proposal to limit number of patients allowed on prior therapy, and stratify analysis
  - Could impose a tighter margin on the prior therapy stratum
  - Require trend towards superiority in the no prior therapy stratum (point estimate in the right direction)
- Should also confirm whether patient characteristics pre-dispose those receiving prior therapy to achieve success

Prior Therapy

- If enrollment and randomization procedures could be streamlined, need for prior therapy may be diminished
- Consider establishing a clinical trial network for this purpose, e.g., NETT
- Advantages:
  - Infrastructure in place for central randomization (e.g., via web portal), EDC, etc.
  - Clinic personnel trained and experienced in anti-bacterial trials
  - Some processes could benefit from commonality across protocols, e.g., informed consent process

Prior Therapy

- Could also consider cluster randomization or community trials
  - Clinics are randomized, rather than patients
  - If all patients in a clinic are randomized to Drug A, it may be possible to accelerate initiation of treatment and avoid need for prior therapy
  - Ideally have a large number of clinics and a small number of patients per clinic
  - Statistical analysis takes into account the impact of clustering; degrees of freedom = # clusters and not # patients
- Trade-off in sample size gain due to reducing prior therapy versus loss due to clustering

Data

- Clintrials.gov: Anti-bacterial studies are under-represented, given mortality risk of infections
- Need to encourage data sharing from studies being run
  - Proposal for CTTI to bring researchers together to share data

Data

- New data collection
  - To aid in non-inferiority margin determination
  - As a source for prior information to support single study submissions or Bayesian approaches
- Options
  - Chart data could be collected from clinics in network to provide historical perspective on practices, patients, etc. (PhRMA proposal)
  - Case control studies to estimate treatment effects
    - Propensity score matching
  - Retrospective cohort studies

Summary

- Emphasis on *evidence*
- Try for superiority; could be embedded in an NI trial
- Bayesian approaches worth considering; caution about exchangeability assumptions
- Cross-infection problem is tricky; need models to interpret variability across sites
- Office of Biostatistics working group to further explore ideas generated from the CTTI meeting

BACK-UP SLIDES

Bayesian Approach

Bayesian alpha calculations using frequentist specs:

$\alpha^* = Pr(H0 | \text{Reject } H0) = A/B$ *(from Bayes' formula),*

where

$A = Pr(H0) \times Pr(\text{Reject } H0 | H0)$

$B = A + Pr(Ha) \times Pr(Ha | Ha)$

The above equation is basically

$$\alpha^* = \alpha / (\alpha + \text{power} \times OS)$$

where

OS = prior odds of success = $Pr(Ha) / Pr(H0)$

α = frequentist alpha

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August 30, 2012

Enrolment Logistics for CABP

BCADD Aug 30, 2012

David Friedland, MD
Vice President, Clinical Sciences
Cerexa, Inc.
A wholly owned subsidiary of Forest Laboratories

Prior to Randomization
Best Case

- ER Triage (10 min)
- Medical history and Physical exam (15 min)
- Blood for chemistry, hematology, blood cultures (10 min)
- Sputum (5 min)
- CXR (30 min)
- High level screening by Study Coordinator (10 min)
  - Confirm diagnosis
  - Check prior medication history
- Informed consent (30 min)
  - Approximately 15 pages
  - Continues to get larger and more complex due to changing ethics and patient confidentiality standards and regulations

Prior to Randomization
Best Case

- Additional lab tests if necessary (2 hours)
  - Liver enzymes, creatinine, etc.
  - Need to wait for results as usually part of inclusion or exclusion criteria, or required for PORT score assessment
- Supplemental medical & surgical history and exam (10 min)
  - All vital signs
  - Pulse oximetry or arterial blood gas
- Urine antigen test (30 min)
- Pregnancy test if applicable
  - No extra time if urine test
  - 2-4 hours if require serum test
- PORT score assessment (15 min)

Prior to Dosing
Best Case

- ECG x 3 (15 min)
- Safety labs if required (10 min)
  - Hematology, chemistry, urinalysis, etc
  - Do not have to wait for results
- Microbiology specimens if required (10 min)
  - Respiratory, blood cultures
- Randomization (20 min)
  - IVRS
- Prepare medication (30 min)

Discussion Points

- Minimum time to receiving study drug is ~ 4-6 hours.
- Preference for PRO use for primary outcome
  - Potentially could add time to enrolment procedures
- Prior antibiotics
  - Daptomycin data suggests prior antibiotics had a masking effect
  - Ceftaroline data suggested similar outcomes; however, on closer inspection, these data actually conflict with daptomycin data
    - Subjects with prior antibiotics randomized to ceftaroline had lower response rates than those with no prior antibiotics
    - No trends using early endpoint where prior antibiotics should have had a more significant effect

Additional Points

- Regulators and clinicians want sicker patients in trials
  - Minimum PORT III but majority IV or V
  - Longer to assess and more likely to have prior antibiotics
    - As was seen with ceftaroline Phase 3 trials
- Diagnostic tests may help identify the “correct” patients
  - Usually do not help with culture results; therefore, no MIC data to help with breakpoints
- Lack of US subjects in Phase 3 trials
  - Even though minority of subjects receive prior antibiotics, US sites do not want to participate if no prior antibiotics allowed
- Clinical Trial Networks could be a solution
  - What about competition if 2 or more Sponsors doing same type of trial?

Brookings Council on Antibacterial Drug Development

Dr. Daniel Benjamin

Professor of Pediatrics and Faculty Associate Director, Duke Clinical Research Institute, Duke University School of Medicine

Two Drug Development Paradoxes

1) For most products, the question is, do they work? And the difference between molecule and placebo can be quite small. In order to power trials and achieve licensure, the incentive is for companies to design ***large*** well-powered efficacy trials that expose many patients to product.

   Antimicrobial drug development paradox: by the time products get to Phase II testing, they probably 'work' (kill the bug on the plate), and the key question is, do they hurt the patient? Adverse events are rarely detected in the setting of small sample size. There is therefore a much greater incentive to design ***small*** trials that show efficacy, but don't reveal safety

2) Skin and soft tissue infections are not a public health crisis, but organisms completely resistant to current antibiotics is.

Challenge is improving safety in the setting of small benefits for many patients in the present, small numbers of patients in the present, and potentially large numbers of patients in the future

Lower the bar for efficacy, raise the bar for safety

- Ease regulatory burden pre-approval: e.g., the fraction of enrollees with prior therapy, sample size, etc.
- Limited indication and/or safety statement (e.g., the safety of this molecule is not well described relative to other therapeutic options for this indication)
- Indication broadened and/or safety statement removed based upon the successful completion of FDA-guided trials designed and powered for safety
- Thus, several hundred fewer patients are tested for efficacy in the current design (no prior antibiotic therapy, etc.) prior to approval in exchange for several thousand more evaluated for safety post-approval
- ‘FDA-guided’ analogous to written request approval for pediatric exclusivity

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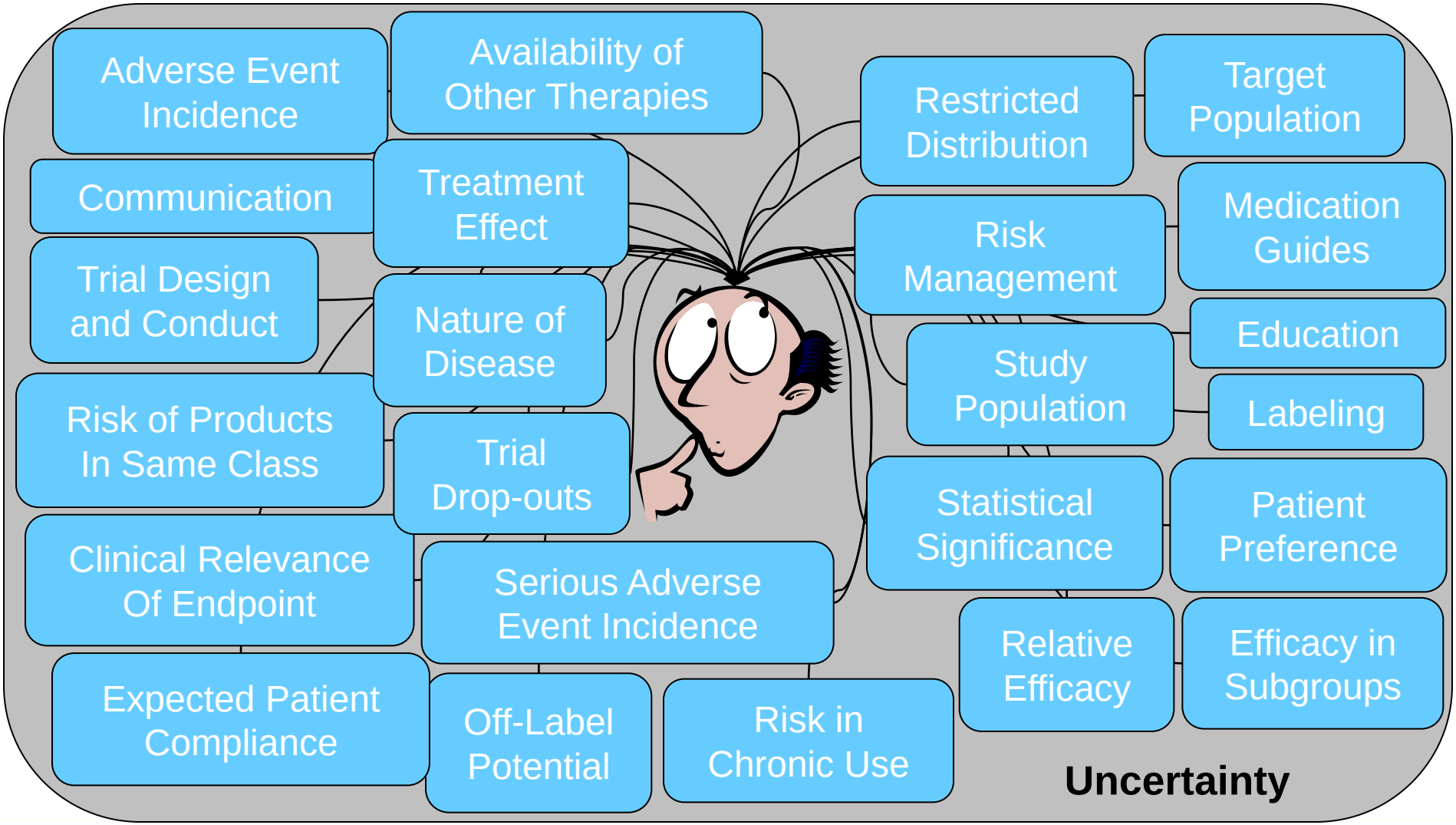
FDA CDER's Benefit-Risk Framework

Theresa M. Mullin, Ph.D.
Director, Office of Planning and Informatics
Center for Drug Evaluation and Research
Food and Drug Administration

What's on the regulator's mind?



A Balancing Act: Judgment vs. Quantitative Analysis

- **CDER's goal was to explore a more systematic approach to benefit-risk assessment**
  - Address the need to clearly communicate a regulator's thinking while respecting their expertise and time
- **We examined formal quantitative methods, but had some concerns**
  - Reducing complex considerations into a single scale cannot capture the nuanced assessments in FDA's decisions
  - Quantitative analysis risks obscuring subjective expert judgment
- **We determined that a structured qualitative approach best fit our needs**
  - Approach best reflects the reality that B-R assessment is a qualitative exercise grounded in quantification of various data
  - Flexible to accommodate more complex supporting quantitative analyses that can aid, rather than replace, expert judgment
  - Clearly communicates the basis for decisions

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Unmet Medical Need	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		

The Rows:
Key Benefit-Risk Considerations

Information on the Therapeutic Area

- Analysis of Condition
- Unmet Medical Need

Product-Specific Information

- Benefit
- Risk

- Risk Management

The Columns: Evidence and Conclusions

Evidence and Uncertainties

- What you know (facts)
- What you don't know (uncertainties and underlying assumptions)
- How good are the data?

Conclusions and Reasons

- What do you make of the data and uncertainties?
- Analysis of the information and its clinical relevance
- Drawing conclusions within each key consideration

Benefit Risk Summary & Assessment – A balanced written analysis of the factors and their tradeoffs that summarizes the resulting regulatory recommendation or action

Benefit-Risk in PDUFA V: FDA's Commitments

- Publish a 5-year plan that describes FDA's approach to implement a structured benefit-risk framework by December 31, 2012 and begin execution by September 30, 2013
- Conduct two public workshops on benefit-risk from the regulator's perspective that will begin by December 31, 2013.
- Develop an evaluation plan to ascertain the impact of the benefit-risk framework.
- Revise review templates, decision memo templates and MaPPs as appropriate to incorporate FDA's approach

Overview of Risk-Benefit within Antibacterial Drug Development

Changing the Paradigm

Ed Cox
Office of Antimicrobial Products
OND/CDER/FDA

Antibacterial Drug Development

- The choices we have before us
- What the impact of these choices might be
- Appropriate balance of risk and benefit and how this may impact antibacterial drug development
- Ultimately how this will impact patients and public health

Background - 1

- Antibacterial drug development programs 1960s 1970s and 1980s. Generally…
  - Trials enrolled patients with infections at any of variety of tissue sites in a trial often with an active comparator
  - Goal of showing comparable point estimates for clinical cure
  - Indications were based on the subsets of tissue sites from within the trials
  - In vitro data (e.g., serum from patients receiving the test drug) also evaluated
  - Indications were less specific than current day (e.g., respiratory tract infection, lower respiratory tract infection, upper respiratory tract infection)

Background - 2

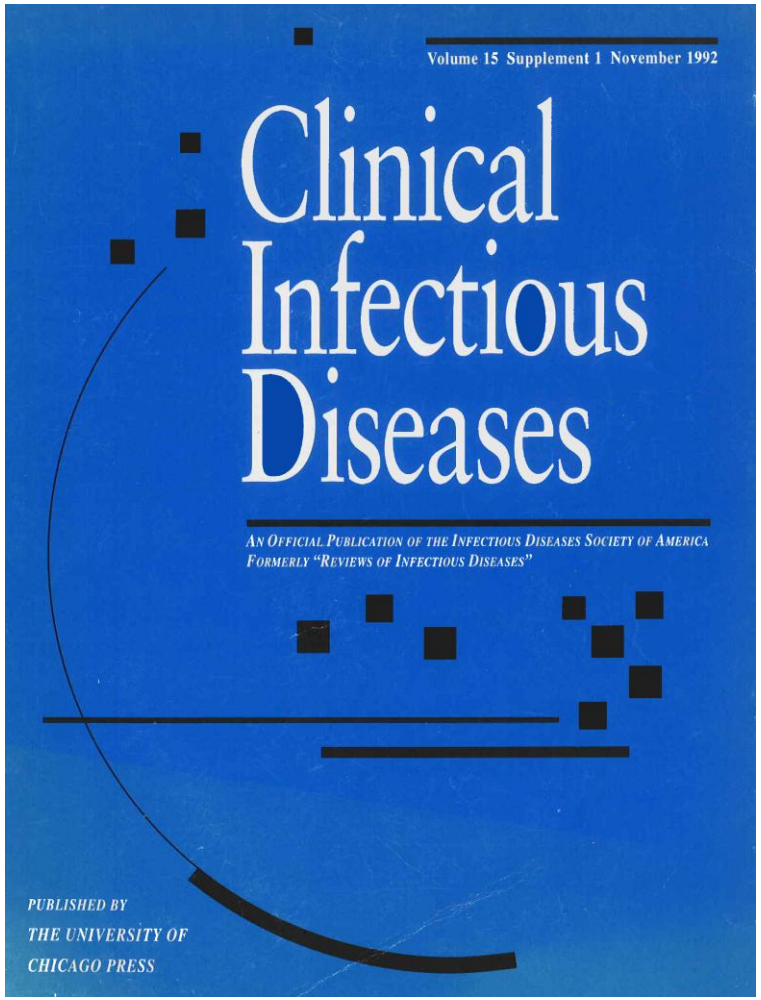
- 1990's move towards more site specific trials
  - Natural history of the disease may differ
  - Endpoints & Treatment duration may differ
- 1992 IDSA Guidelines
- 1992 FDA Points to Consider document – Clinical Development and Labeling of Anti-Infective Drug Products*
- 1998 FDA Guidance documents**
- Present – Updating Guidance documents
  - 10 indication-specific plus others updated so far**

* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070975.pdf

** http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm

1992 IDSA/FDA Guidelines

There was a clear need to improve the design and conduct of clinical trials of anti-infective drugs; more specifically, it seemed essential to (1) provide clearer definition of disease states and their clinical and microbiological endpoints; (2) take into account changes in the diagnosis and management of specific infectious diseases; …



Background - 3

- 2000 Greater emphasis on the evidence base for non-inferiority trials
  - Public concern about the scientific validity of antibacterial drug trials
- This has generally led to larger trials
- Continued trend towards more specific Indications

Respiratory tract infection (RTI)

Lower RTI + Upper RTI (ABS and ABOM)

CABP + ABECB +/- Nosocomial pneumonia

HABP + VABP

Drug Development - 1

- Decline in activity in the development of new antibacterial drugs
- Mature field w/ approx. 50 to 60 different active ingredients
  - Some no longer marketed
  - Some had postmarket safety problems
  - Some may not have had characteristics that would lead to their continued availability
  - Resistance has impacted upon utility of some

Drug Development - 2

- Is the current level and are the types of antibacterial drugs that are being developed meeting patient and public health needs?
  - Currently we are seeing areas of unmet need
  - Resistance continues to erode our therapeutic armamentarium
  - Importance of
    - Development of new safe & effective antibacterial drugs
    - Antimicrobial stewardship – prudent use
    - Infection control

Drug Development - 3

- Advances in clinical trials intended to improve the science of clinical trials
  - Comments on lack of feasibility
  - Economic issues in antibacterial drug development
- Pipeline of new antibacterial drugs not robust and focused on a limited disease spectrum
  - Some for skin infections, little for CIAI, CUTI, very little for CABP & HABP / VABP
- Some antibacterial drug development in important bacterial diseases reportedly going ex-U.S.

Addressing Patient and Public Health Needs

- How do we address patient and public health needs for antibacterial drug to treat patients' infections?
- What are some of the choices and/or trade-offs?
- How should these be addressed?

Goals – Theory and Practice

- Most would want
  - A robust pipeline of new antibacterial drugs – especially drugs with new mechanisms of action
  - Precise characterization of safety and efficacy
  - Agents already available that are active against new resistance mechanisms that will emerge in the future
  - Little uncertainty
- All of these goals may not be achievable
  - economic, scientific, regulatory issues/challenges
- Development of a new drug can take 5-10 years
  - Difficult to react in a timely fashion
  - Some development programs not successful
  - Ideally have options to choose from in advance of the need

Questions on the Issues and Challenges we Currently Face

- Are there ways that we can do a better, more efficient job with clinical trials?
- If a greater tolerance for risk and uncertainty is appropriate, in what areas?
  - areas of unmet need?
  - indications where development is sparse?
  - other indications?
- Why might one consider a greater tolerance for risk and uncertainty?
  - Unmet need? Lack of satisfactory options? Feasibility? Characteristics of the product?
- If accepting greater uncertainty is appropriate, we may learn important information about a product in the postmarketing setting (e.g., new safety findings, settings where efficacy may be relatively less than other products); will that be acceptable?

A Somewhat Paradoxical Situation

- Achieving precise characterization of efficacy and safety for traditional antibacterial drug development may lead to less antibacterial drug development and generate unmet need
- Once there is unmet need, greater risk and uncertainty may be accepted for the unmet need population
- It is somewhat paradoxical that the avoidance of uncertainty for traditional development programs is generating the situation that leads one to be willing to accept uncertainty for the unmet need scenario

A Somewhat Paradoxical Situation

- Generating unmet need also means that there is a period of time when we lack satisfactory treatment options for patients
- Addressing unmet need, while a critical thing to do once it has developed, is a situation of trying to catch up with what has already happened (resistance)
- Ideally new agents would already be available and we could avoid the unmet need scenario

Theoretical Scenarios on Drug Development – Precision and Uncertainty

- High levels of precision (lower uncertainty) may lead to few new antibacterial drugs developed for a limited range of indications that are very well characterized
  - unmet need may persist
- Lower levels of precision (higher uncertainty) may lead to more antibacterial drugs developed for more indications, but they will be less well characterized –
  - could possibly avoid an unmet need scenario(s)
- There are many points in between these two poles and what is appropriate likely varies by indication
- Some of the new drugs that are developed may add significantly to the therapeutic armamentarium, others may not add much
- Important to articulate judgments and trade-offs in an open and transparent manner

Point for Discussion

- We welcome a discussion on the issue of appropriate balance of risks, benefits, and uncertainty in order to best meet patient and public health needs.

- Thank you

Benefit/Risk in the Context of Infections Caused by Treatment Resistant Pathogens

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Brookings Council on Antibacterial Drug Development

August 30, 2012

Disclosures: I am an employee of GlaxoSmithKline

Benefit/Risk evaluations are sometimes required when information is limited

- Regulatory science (like clinical medicine) requires making life or death decisions based on imperfect information
  - Consider “Best Available Therapy” for untreatable infections
- Science will not be able to give us the definitive answers we want, because the definitive scientific studies (randomized, placebo-controlled trials) cannot be done
- Approaches have accommodated these challenges in settings of high unmet medical need
  - Animal rule for Biothreat pathogens
  - Emergency use authorization for IV Relenza during the 2009 influenza pandemic
  - Approval of last line therapies in oncology on very limited datasets
- Streamlined development programs speed product availability but increase uncertainties
  - Addressing unmet need provides a larger benefit that can, to some degree, offset residual uncertainty or risk
    - This is an area where doctors and patients may accept greater risk
    - This is also an area where doing nothing can actually be more harmful
- **We are now facing a crisis with few/no effective antibiotics to treat severe infections caused by resistant pathogens**

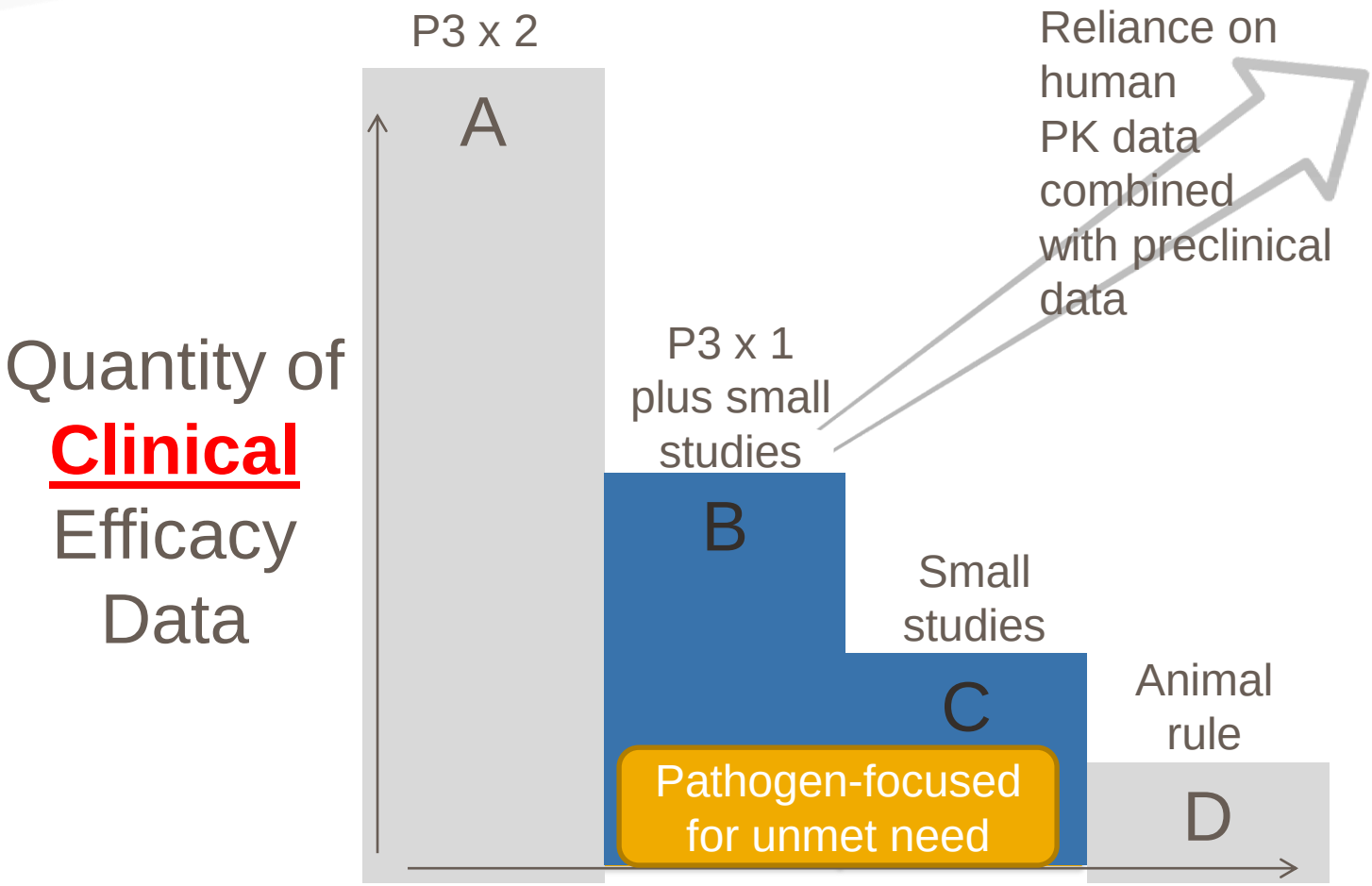
Impact of Antibiotics on Serious Infections—Potential for a Large Clinical Benefit

Disease	Death Pre-Antibiotics	Death With Antibiotics	Change in Death
Community Pneumonia[1]	~35%	~10%	**-25%**
Hospital Pneumonia[2]	~60%	~30%	**-30%**
Heart Valve Infection[3]	~100%	~25%	**-75%**
Brain Infection[4]	>80%	<20%	**-60%**
Skin Infection[5]	11%	<0.5%	**-10%**

[1]IDSA Position Paper '08 Clin Infect Dis 47(S3):S249-65; [2]IDSA/ACCP/ATS/SCCM Position Paper '10 Clin Infect Dis In Press; [3]Kerr AJ. Subacute Bacterial Endocarditis. Springfield IL: Charles C. Thomas, 1955 & Lancet 1935 226:383-4; [4]Lancet '38 231:733-4 & Waring et al. '48 Am J Med 5:402-18; [5]Spellberg et al. '09 Clin Infect Dis 49:383-91 & Madsen '73 Infection 1:76081

Addressing unmet need via Four Tiers

A & D are familiar, B & C are new



Acceptance of smaller clinical datasets (often merged across body sites) in response to unmet medical need

ENGELBERG CENTER for Health Care Reform at BROOKINGS

Brookings Council on Antibacterial Drug Development

Meeting #1

The Brookings Institution

August 30, 2012