DEVELOPING AND EVALUATING YOUR INTERVENTION

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SHEA ANTIMICROBIAL STEWARDSHIP RESEARCH WORKSHOP

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Duke University School of Medicine

dcasip.medicine.duke.edu

Duke Center for Antimicrobial Stewardship and Infection Prevention

Disclosures

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Borrowed Slides: Tamar Barlam; Julie Szymczak

Objective: Develop and Evaluate Interventions

Outline key aspects of stewardship intervention design to consider before implementation to optimize research success

Describe implementation strategies that will aid in more systematic assessment of stewardship initiatives

Goals for Stewardship Researchers

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1] Sara E. Cosgrove,[2] Lilian M. Abbo,[3] Conan MacDougall,[4] A[illegible]y N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenk[illegible][12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A.[illegible]hl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

Provide a guideline that diverse stakeholders find useful

More detailed, implementation-oriented focus compared with prior guidelines

Use the GRADE system to rank the guideline's recommendations and the level of evidence

My work here…

Slide: Dr. Tamar Barlam, Boston Univ

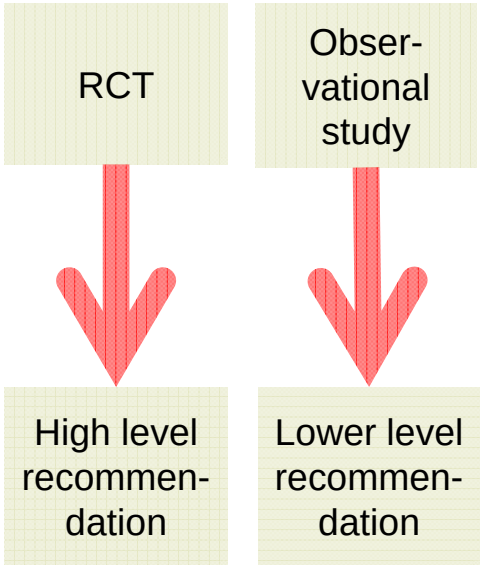
GRADE and PICO

Develop PICO questions to frame topics

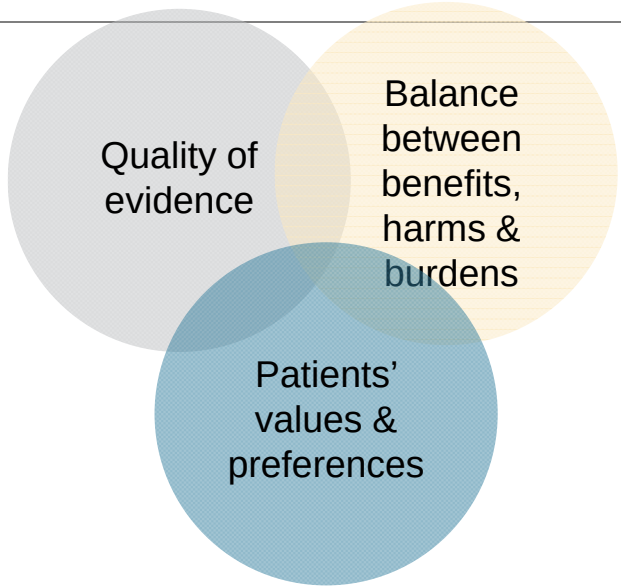
- Population of interest
- Intervention or indicator
- Comparator or control group
- Outcome

Slide: Dr. Tamar Barlam, Boston Univ

From evidence to recommendations



Old system



Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Slide: Dr. Yngve Falck-Ytter and Dr. Tamar Barlam

GRADE

Quality of Evidence

GRADE: all evidence may be examined

If there is a question, then there is evidence

Lack of RCTs does not mean weak evidence

Higher quality indirect data may be preferable than low quality direct data

Slide: Dr. Yngve Falck-Ytter and Dr. Tamar Barlam

Your Charge…

Research that can help inform stewardship practice

Qualitative and quantitative implementation scientific inquiry

Hopefully, the next revision of this guideline will have many more strong recommendations as the quality of the evidence improves

Slide: Dr. Tamar Barlam, Boston Univ

Homework: Read *ICHE*

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

SHEA WHITE PAPER

Research Methods in Healthcare Epidemiology and Antimicrobial Stewardship

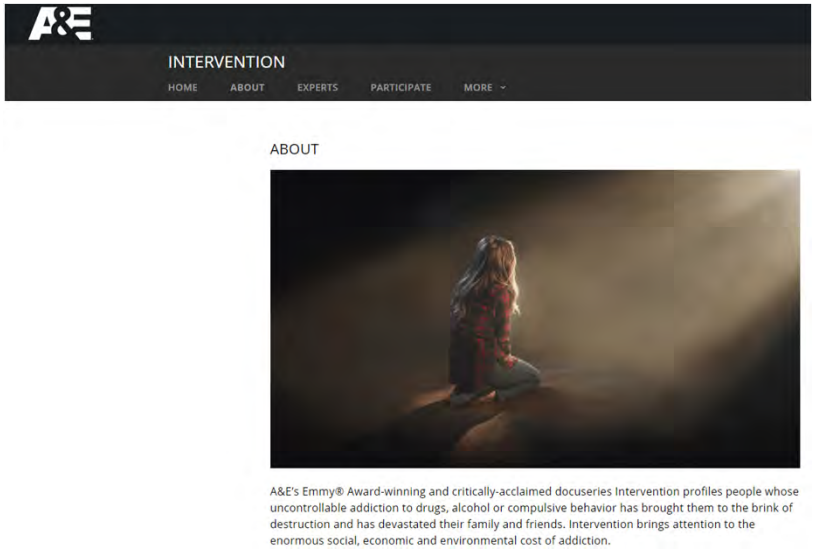
Daniel J. Morgan, MD, MS;[1,2] Nasia Safdar, MD, PhD;[3,4,5] Aaron M. Milstone, MD, MHS;[6] Deverick J. Anderson, MD, MPH[7]

Topics, published in *ICHE* 2016

- Randomized Controlled Trials
- Quasi-experimental Designs
- Use of Administrative and Surveillance Databases
- Survey and Qualitative Research
- Observational Studies
- Mathematical Modeling

What does it mean to intervene?

"Look, just relax, son . . . relaaaaaaaax . . . I'm gonna come over there now and you can just hand me your gun. . . . Everything's gonna be reeeal cool, son."



What does it mean to intervene in antimicrobial stewardship?

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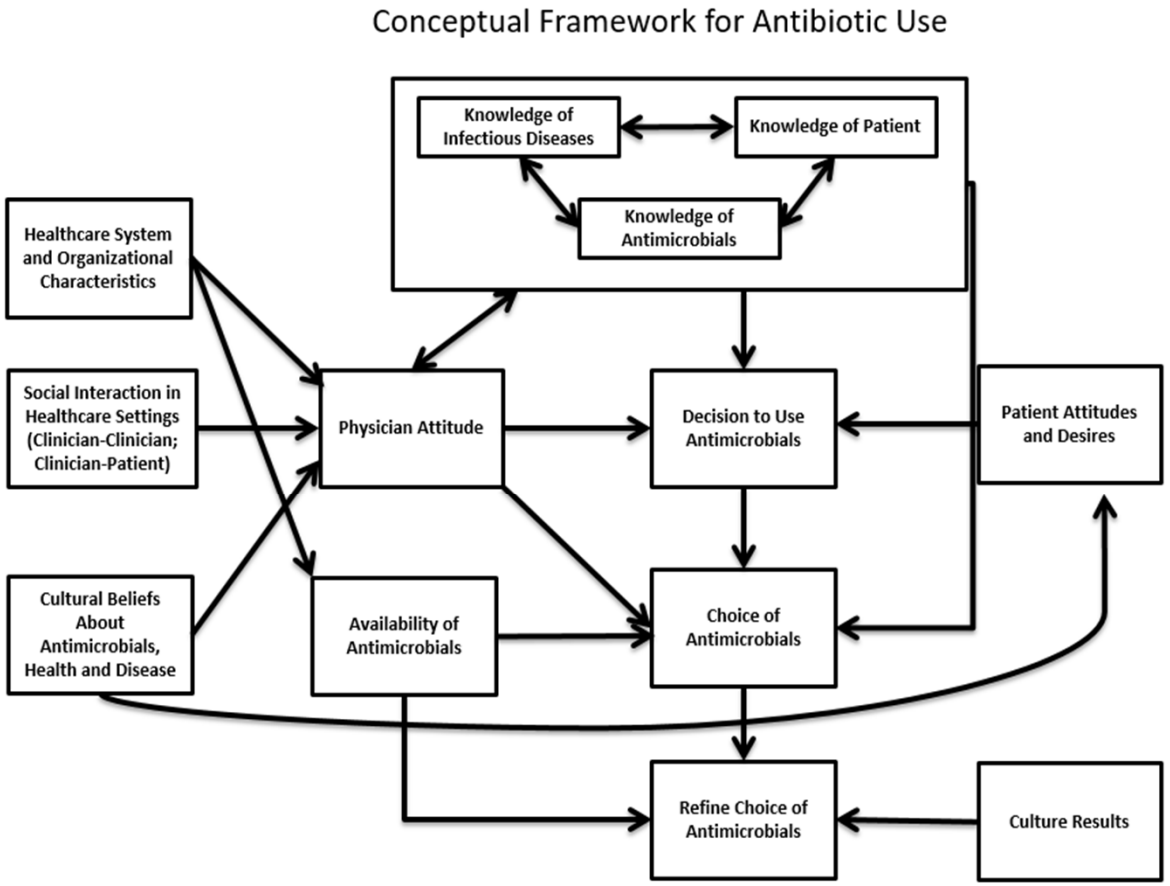


Source: *Szymczak and Newland (Forthcoming) "The Social Determinants of Antimicrobial Prescribing: Implications for Antimicrobial Stewardship." Practical Implementation of an Antimicrobial Stewardship Program, SHEA*

Innovation

The best ideas are the most simple and easy to explain

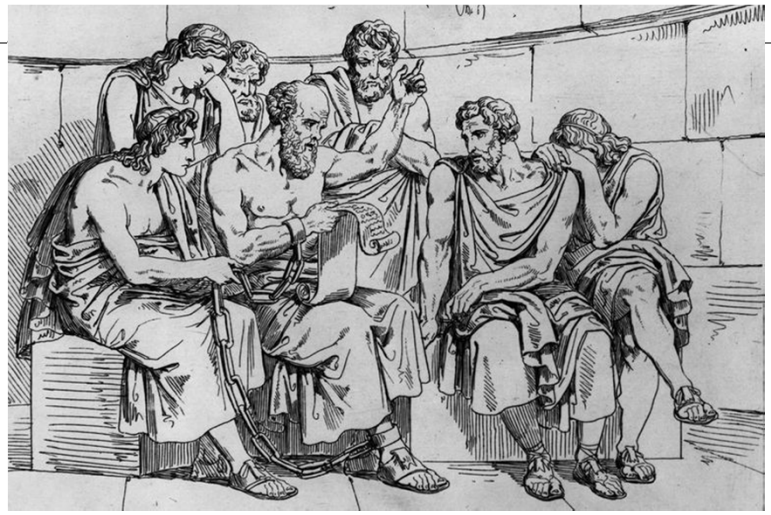
Plausibility

Adaptation from another field or prior study

<u>Tips:</u>

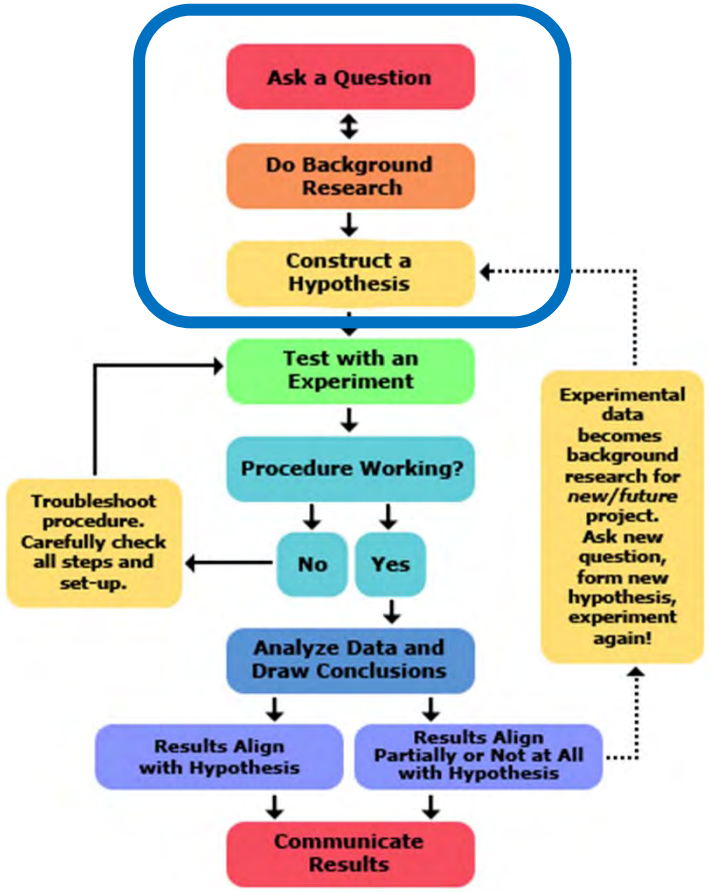
Talk it through with your team and collaborators

Keep a running list

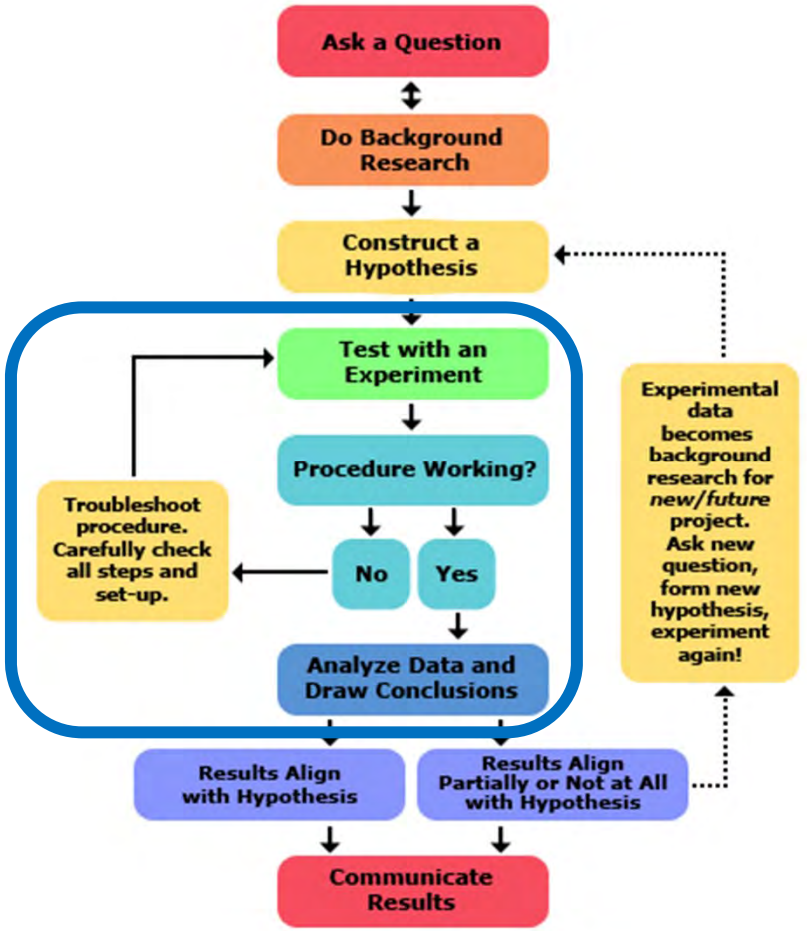


A form of cooperative argumentative dialogue between individuals, based on asking and answering questions to stimulate critical thinking and to draw out ideas and underlying presumptions.

Nosce te ipsum



The Scientific Method



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Nosce te ipsum: What are your goals?

Intervention development or Pilot

Efficacy and effectiveness studies

Implementation studies

Will it float?

Can it work?

Can it be applied?

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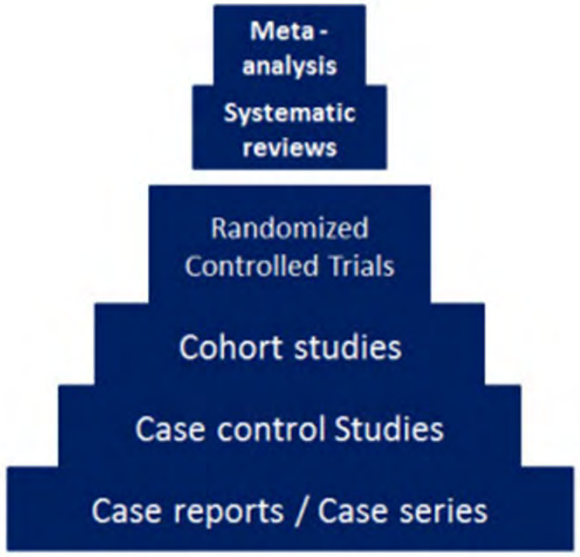
Nosce te ipsum: What are your goals?



Experimental Studies:
Randomized Controlled Trials
Quasi-experimental Studies

Observational Studies:
Cohort Studies
Case Control Studies
Cross-Sectional Studies
Ecologic studies
Case Series

Establish causality

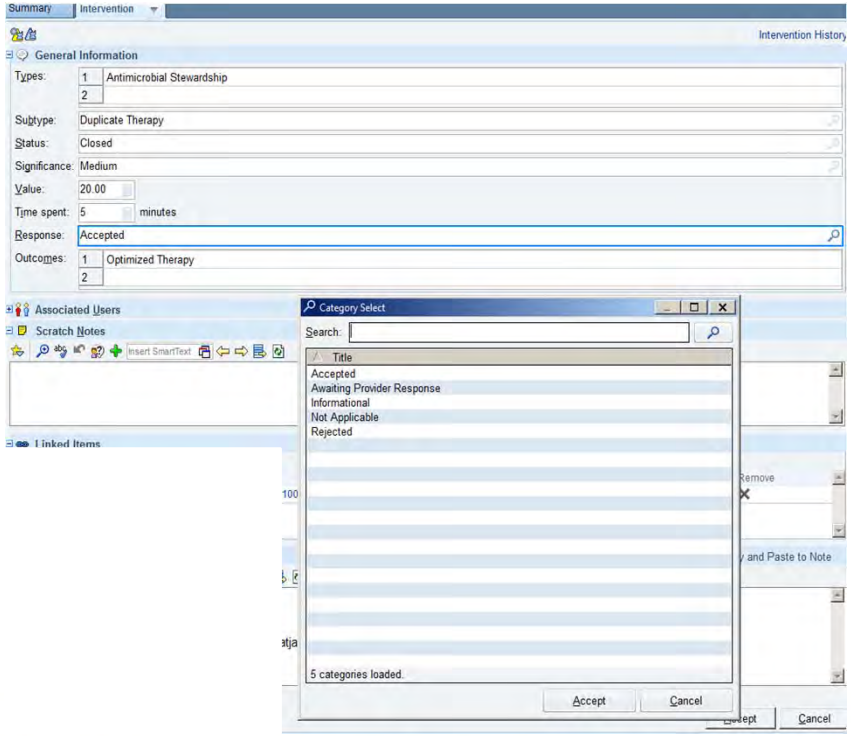
Observe Associations

Generate Hypothesis

Duke University Medical Center Library and Archives. http://guides.mclibrary.duke.edu/ebm/studydesign Accessed 11-1-2016.

Nosce te ipsum: What is the targeted process and setting?

- Observe
- Socio-behavioral factors
- Review problem and possible interventions with front-line stakeholders
- Understand operational issues



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Nosce te ipsum: What is the targeted process and setting?

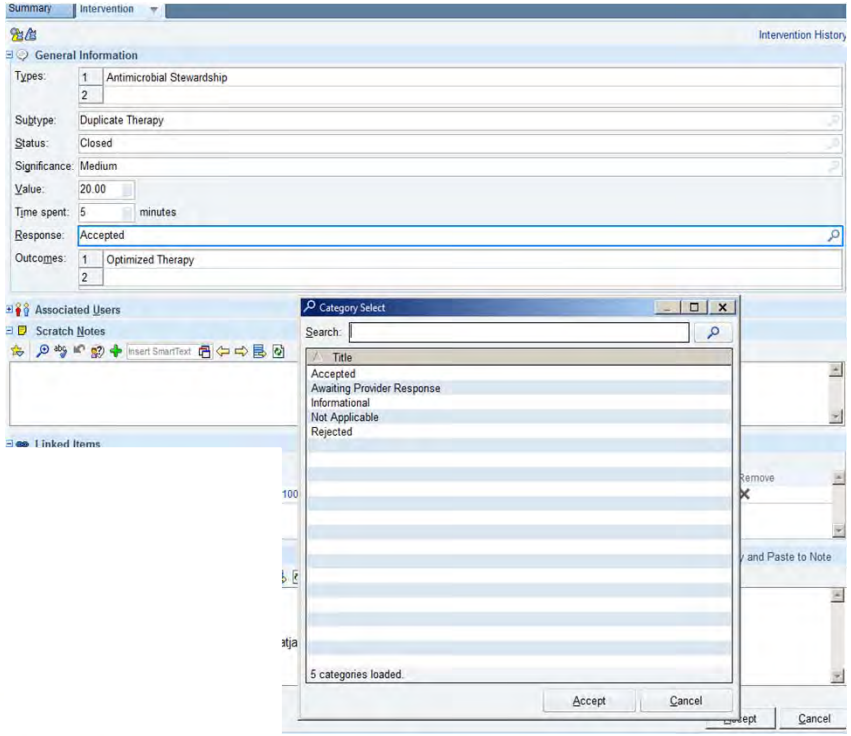
Observe

Socio-behavioral factors

Review problem and possible interventions with front-line stakeholders

Understand operational issues

Response		
Missing	441	54%
Accepted	207	25%
Awaiting Provider Response	10	1%
Informational	136	17%
Not Applicable	3	0%
Rejected	19	2%



Process: Anticipate setbacks, elicit feedback

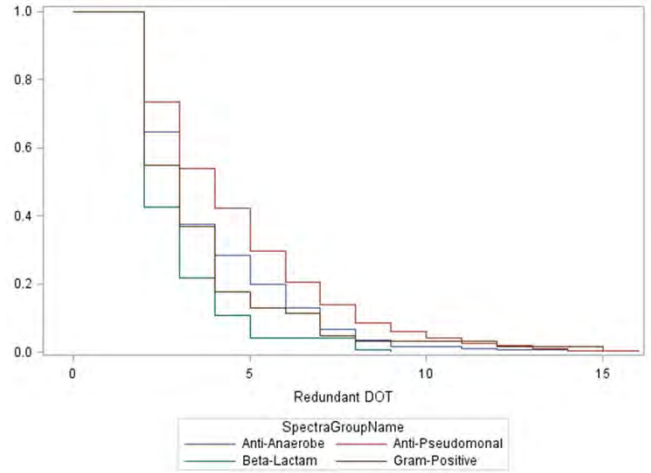
How burdensome would the proposed change in process be? What can you do to minimize that burden?

Allow some flexibility

How will data collection fit in?

Careful research, revision, and vetting of the “products” and data collection tools

Redundant Events by spectrum group			
Anti-pseudomonal	220 (38)	1010	4 (2-6)
Anti-anaerobe	176 (30)	668	3 (2-5)
Gram-positive	62 (11)	221	3 (2-4)
Beta-lactams	120 (21)	346	2 (2-3)



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Protocol Writing

Aims

Setting

- Where
- Who
- When

Procedures

- What
- Allocation
- If… Then…

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TABLE OF CONTENTS

Assessment (and dissemination) plan

Outcome selection

- Primary vs. secondary
- What matters to those involved in the process?

Primary comparison

- After you do it, what does it mean?
- Confounding, selection, measurement biases et al.

Design

IRB, consideration of benefits/risks

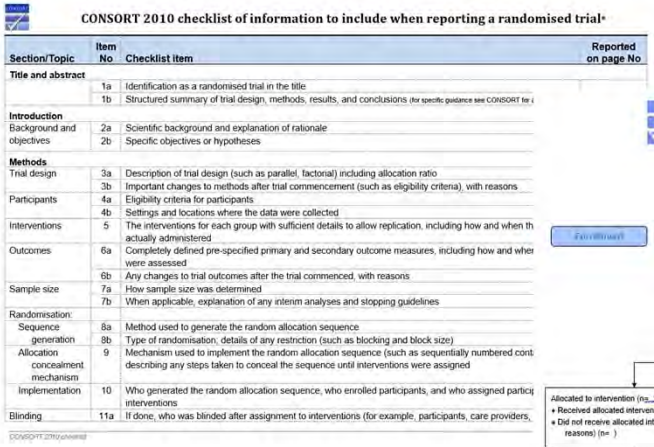
Data Management

Statistical plan

- Sample size

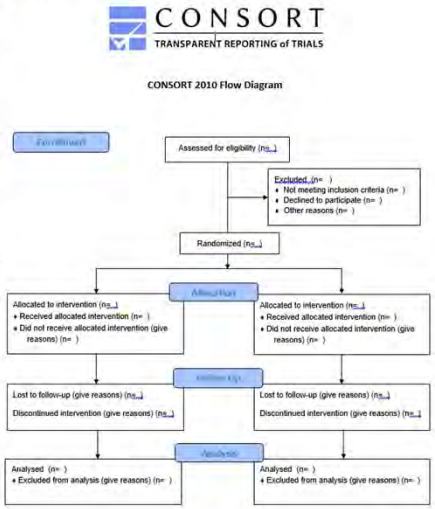
CONSORT

Consolidated Standards of Reporting Trials



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when th actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and wher were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation, details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered cont describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned partici interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers,	



http://www.consort-statement.org/

CONSORT 2010 Key Documents

- CONSORT 2010 Checklist
- CONSORT 2010 Flow Diagram
- CONSORT 2010 Statement
- CONSORT 2010 Explanation and Elaboration Document

TREND

Transparent Reporting of Evaluations with Non-randomized Designs

Improving the Reporting Quality of Nonrandomized Evaluations of Behavioral and Public Health Interventions: The TREND Statement

Developing an evidence base for making public health deci- | Don C. Des Jarlais, PhD, Cynthia Lyles, PhD, Nicole Crepaz, PhD, and the TREND Group

American Journal of Public Health 94, no. 3 (March 1, 2004): pp. 361-366.

TABLE 3. Checklist of Key Considerations When Developing a Quasi-Experimental Study

CONSIDERATIONS FOR RETROSPECTIVE AND PROSPECTIVE QUASI-EXPERIMENTAL STUDIES
1. Determine PICO: population, intervention, control group, outcomes (specify primary vs secondary outcomes)
2. What is the hypothesis?
3. Is it ethical or feasible to randomize patients to the intervention?
4. Will this be a retrospective or prospective study or a combination of both?
5. What are the main inclusion and exclusion criteria?
6. Will anyone (participants, study staff, research team, analyst) be blinded to the intervention assignment?
7. Consider options for control group
8. Consider options for nonequivalent dependent variable
9. How will the observations (outcomes) be measured?
10. How many observations can be measured before and after intervention?
11. How should the observations be spaced to account for seasonality? Weekly? Monthly? Quarterly?
12. Do you hypothesize that the intervention will diffuse quickly or slowly? (Eg, are changes in the outcomes expected right away or only after a phase-in period?)
13. Do you hypothesize that the intervention will have a lasting effect on the outcome? (If yes, do not use crossover design.)
14. What is the analysis plan? (Consult a statistician.)
15. If the unit of analysis differs from the unit of assignment, what analytical method will be used to account for this (eg, adjusting the standard error estimates by the design effect or using multilevel analysis)?
16. What sample size is needed to be powered to see a significant difference? (Consult a statistician.)
17. Will the analysis strategy be intention to treat or how will noncompliers be treated in the analysis?
ADDITIONAL CONSIDERATIONS FOR QUASI-EXPERIMENTAL STUDIES WITH PROSPECTIVE COMPONENTS
18. What will be the unit of delivery (eg, individual patient or unit or hospital)?
19. How will the units of delivery be allocated to the intervention?
20. Who will deliver the intervention (eg, study team or healthcare workers)?
21. How and when will the intervention be delivered?
22. How will compliance with the intervention be measured?
23. Will there be activities to increase compliance or adherence (eg, incentives, coaching calls)?

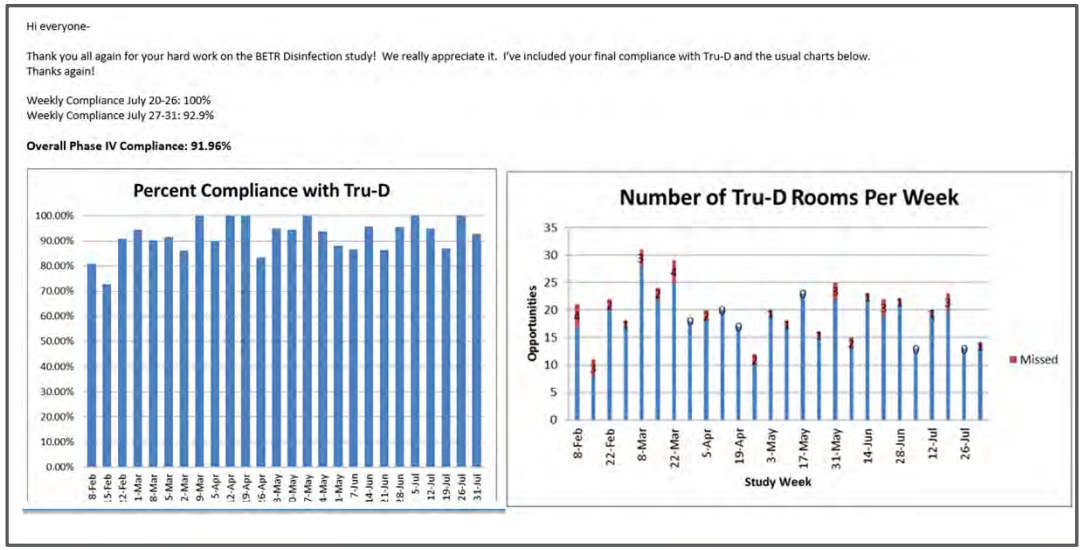
Infect Control Hosp Epidemiol 2016;37:1135–1140

Is the procedure working?

Process measurement

Regular process data feedback to those involved

Make a goal and incentivize



Pilot and perfect:

- Estimates of sample size
- Dry runs
- Staggered roll out
- Collaboration during the study

Nosce te ipsum: What are the limitations?

How was randomization accomplished and was it effective?
- Contamination of study arms
- Selection or confounding bias

Outcome definition/ascertainment
- Loss to follow up

Adequately powered?

How well was study protocol followed?
- Insufficient documentation/data collection
- Insufficient implementation data

Could study protocol be implemented in other practice settings?
- Generalizability
- Applicability
- External validity

Special Considerations for interventional antimicrobial stewardship research

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Cannot blind

- Contamination and selection bias

Cannot deliver intervention without policy/system/practice change

- Unit of analysis
- Comparator

Don’t want to (or can’t) enroll/consent patients

Special Considerations for interventional antimicrobial stewardship research

Cannot blind

- Contamination and selection bias

Cannot deliver intervention without policy/system/practice change

- Unit of analysis
- Comparator

Don’t want to (or can’t) enroll/consent patients

<u>Solution(s):</u>

Cluster trials: randomize to groups (units, practices, hospitals) instead of enrolling individuals (patients or providers)

Stepped Wedge: random and sequential crossover of clusters from control to intervention until all clusters are exposed

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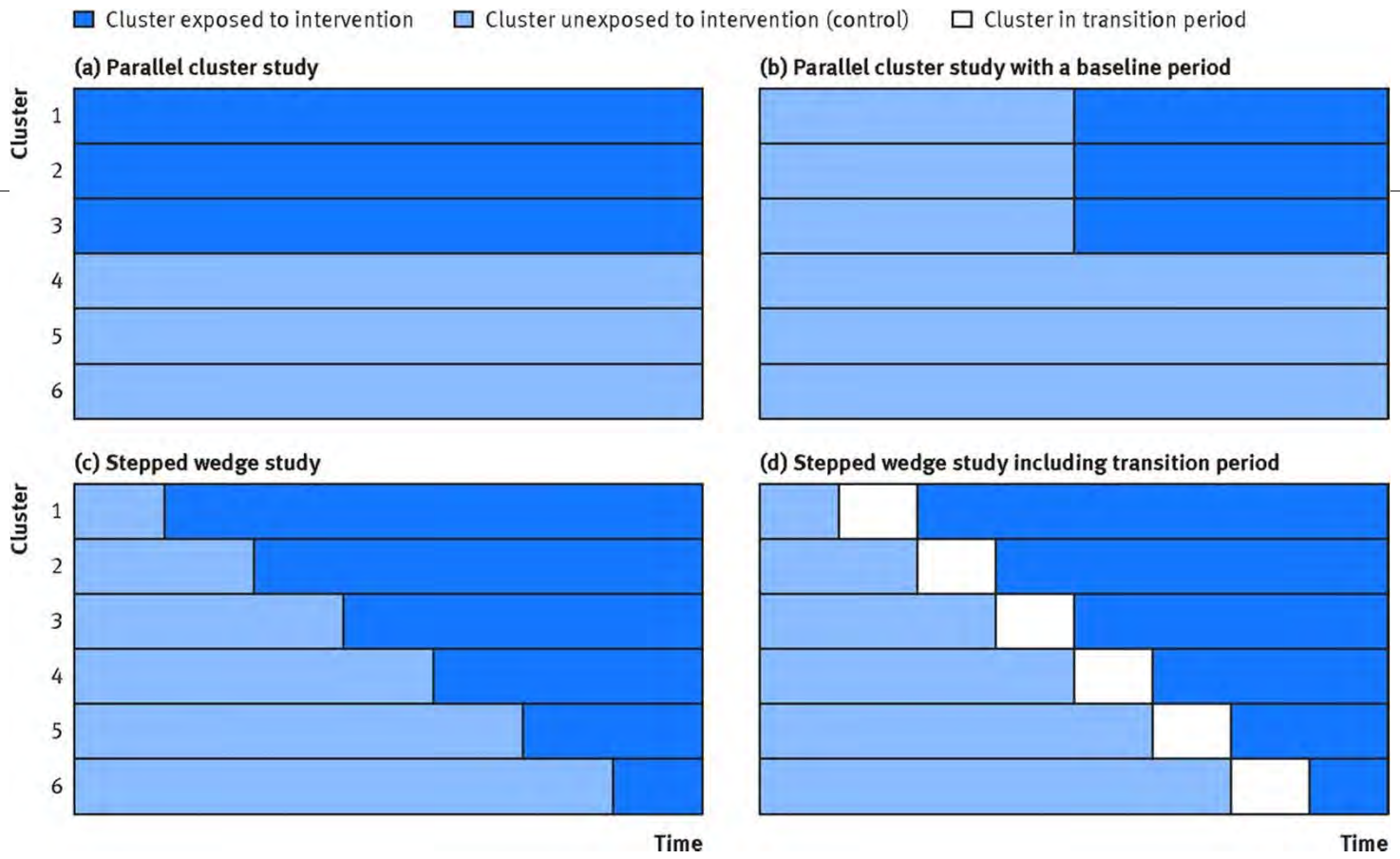

BMJ 2015;350:h391

Special Considerations for interventional antimicrobial stewardship research

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Lack of generalizability

- Single center study

Special Considerations for interventional antimicrobial stewardship research

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Lack of generalizability

- Single center study

<u>Solution(s):</u>

State in limitations, realize that the findings apply best to populations similar to your study

- Is there something that makes your study population special?

Make Table 1 a practical one

Describe baseline ASP implementation, rates, or “control” arm well

Special Considerations for interventional antimicrobial stewardship research

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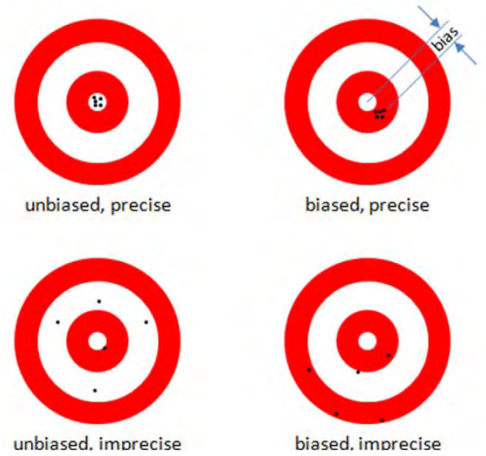
Bias/Confounding



- By patient subgroups

Special Considerations for interventional antimicrobial stewardship research

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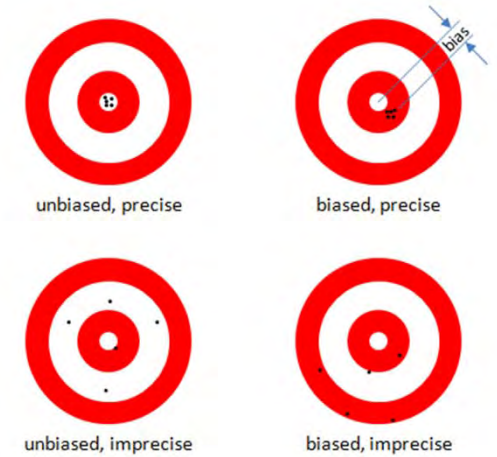
Bias/Confounding



<u>Solution(s):</u>

Anticipate possible confounders

Measure them:

- Stratified randomization of the intervention
- Demonstrate they are “even” (or not differential) during both arms
- Add an additional control?

How much of your intervention effect might be biased?

- Post-hoc analyses – subgroups or sensitivity analysis
  - By Site
  - By patient or provider characteristic

Special Considerations for interventional antimicrobial stewardship research

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Limitations of AU rates as a primary outcome

$$\frac{\text{DOT}}{\text{Patient days}\ \text{Days present}}$$

Special Considerations for interventional antimicrobial stewardship research

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Limitations of AU rates as a primary outcome

$$\frac{\text{DOT}}{\text{Patient days}}$$

Days present

Seasonality

Solution(s):

- Use a whole year of data in baseline/intervention periods
- Compare to similar season in baseline period
- Adjust for month/season in regression or ITS
- Plan cross overs wisely

Denominators

Solution(s):

- Make sure to report LOS
- Deal with early death
- DOOR/RADAR?

Final Thoughts

Study designs of any type can have impact on AS, as long as they are done well.

AS, as a field, requires study designs that address implementation as well as effect.

Read and utilize SHEA White Papers on Research Methods.

Think through study limitations during intervention development and delivery.

Continue to question!