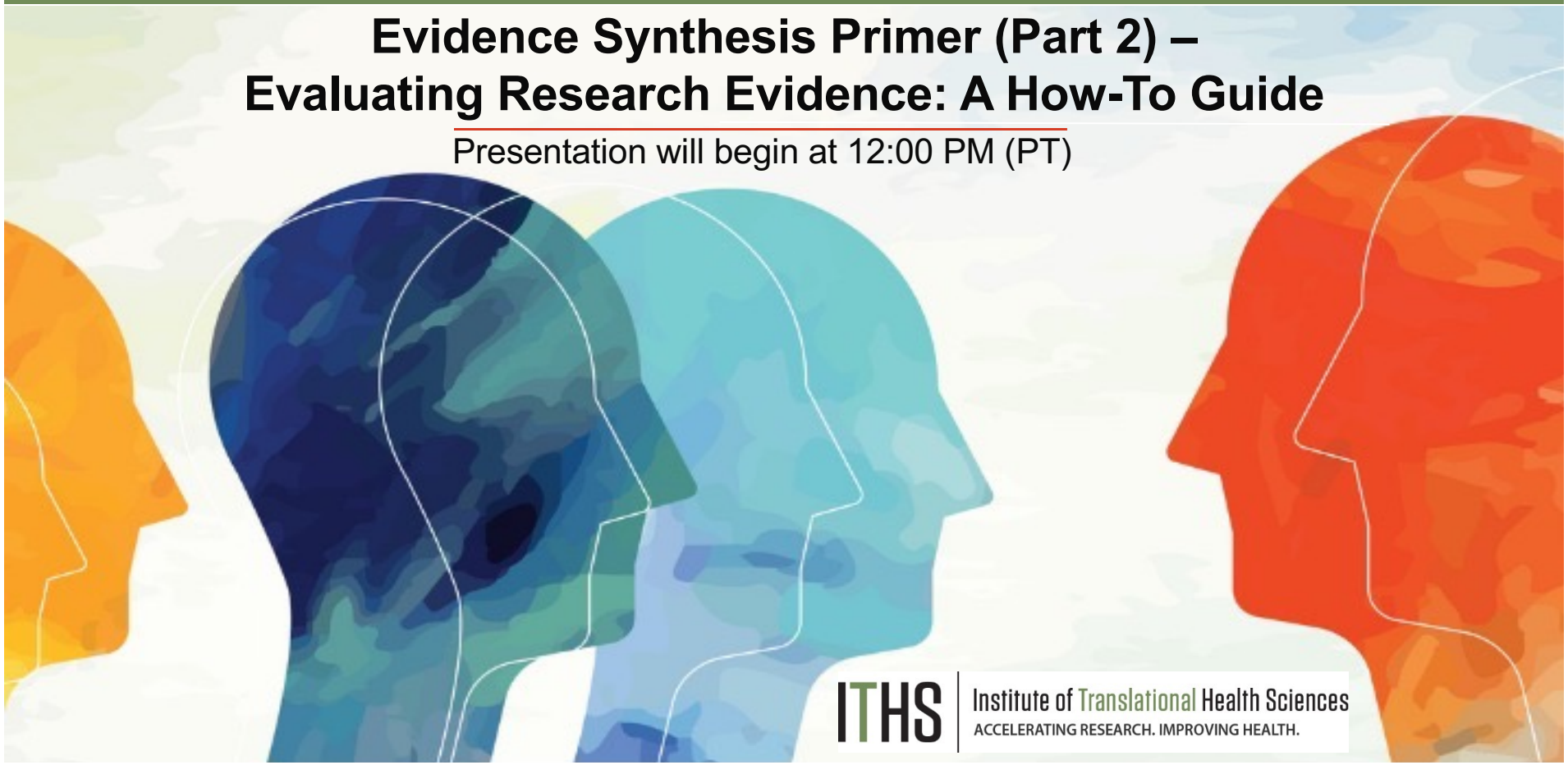
Career Development Series 2021

Evidence Synthesis Primer (Part 2) – Evaluating Research Evidence: A How-To Guide

Presentation will begin at 12:00 PM (PT)



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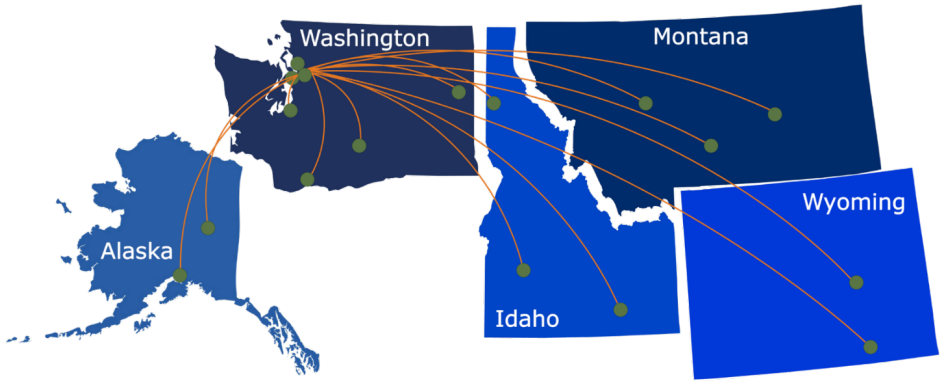


What We Offer:

1. **Research Support Services:** Members gain access to the different research services, resources, and tools offered by ITHS, including the ITHS Research Navigator.

2. **Community Engagement:** Members can connect with regional and community based practice networks

3. **Education & Training:** Members can access a variety of workforce development and mentoring programs and apply for formal training programs.

4. **Funding:** Members can apply for local and national pilot grants and other funding opportunities. ITHS also offers letters of support for grant submissions.

Contact our Director of Research Development

- **Project Consultation**
- **Strategic Direction**
- **Resources and Networking**

Melissa D. Vaught, Ph.D.
ithsnav@uw.edu
206.616.3875

Feedback

At the end of the seminar, a link to the feedback survey will be sent to the email address you used to register.

Career Development Series 2021

Evidence Synthesis Primer (Part 2) – Evaluating Research Evidence: A How-To Guide

Presented by Kenn B. Daratha, PhD

Providence Sacred Heart Medical Center
Gonzaga University Nurse Anesthesia Program

ITHS | Institute of Translational Health Sciences
ACCELERATING RESEARCH. IMPROVING HEALTH.

Learning Objectives

Attendees will be able to :

1. Conduct an a-priori power analysis

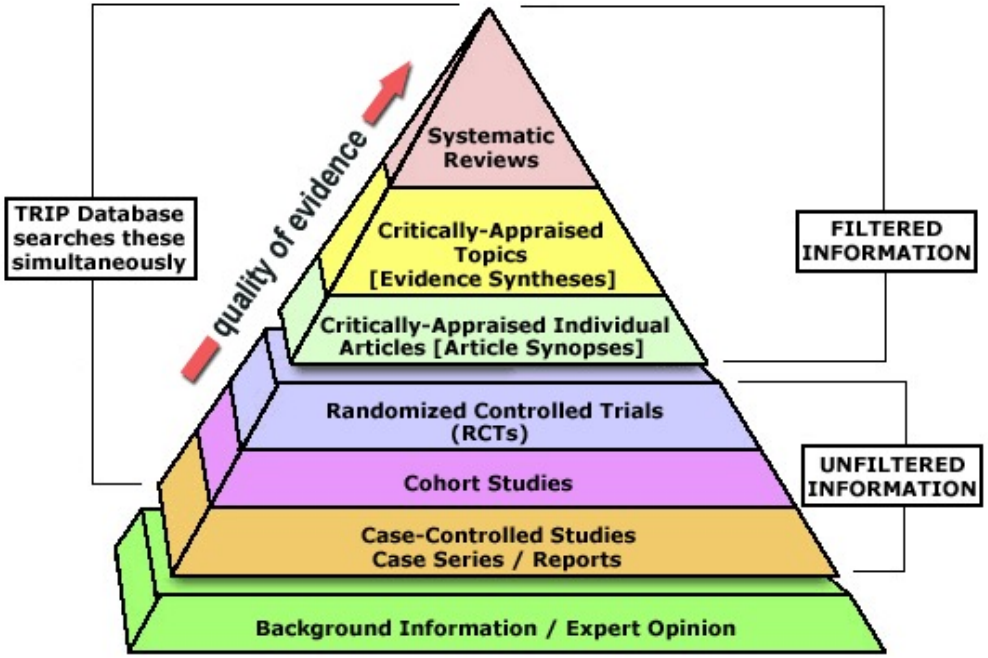
2. Critically evaluate a treatment study

Clinical Questions

Most clinical questions arise when observing variability in practice:

- Long held beliefs
- Learned during our training
- Success stories of our colleagues
- Publication
- We have always done it that way
- Compelling evidence forces us to consider an intervention

Evidence Pyramid



Evidence Synthesis Primer (Part 1)

- Clinical Question (PICO Format)
- Cochrane Review Groups
- Medline Searches (MeSH Terms)
- Evidence Catalogs
- Evidence Flow Diagrams
- Summary Table of Evidence
- Evidence Synthesis

Career Development Series 2021

Critically Appraised Topic

Evidence Synthesis Primer (Part 2)

Reviewer Name:	Answer Key	
Review Date:	05/21/2020	
PMID:	32160661 (Barrot)	
Journal Article Title:	Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. (2020)	
Clinical Question:	Among patients with acute respiratory distress syndrome (ARDS) does conservative vs. liberal oxygen therapy improve all-cause mortality at 28 days.	
Clinical Question Type:	☒	Treatment
	☐	Diagnosis
	☐	Prognosis
	☐	Systematic Review/Meta-Analysis
Study Design:	Prospective, randomized open label study.	
Sample Size and Power:	850 patients 90% between group a priori power analysis based on an expected effect size of 9% from published results of two prospective trials 396 were eligible, 191 were excluded: 205 randomized Trial stopped by the DSMB for increased adverse risk in the conservative oxygenation group.	
Validity Assessment:	Criteria	Assessment
	Randomization	Computer randomization stratified by center, age, and severity of respiratory failure
	Blinding	Open Label (not blinded based on impossibility of making treatment assignment)
	Baseline Group Comparability	Groups were comparable based on review of Table 1
	Follow up	Survival curves indicate patients were followed up to 90 days after surgery. Four patients our of 205 randomized were excluded from analysis (2%).
	Intent to Treat	Analyses were performed in the intention to treat population, defined as all patients who underwent randomization minus exclusions.
Validity Summary:	After examining randomization, baseline group comparability, follow up and intent to treat, this study was determined valid for informing practice. While the study was not blinded, the open label nature of this experiment did not likely change study outcomes.	

- Read and assess each full-text article you have chosen to include in your review
- I record my assessment findings in a critically appraised topic (CAT)
- Assess design, power, study validity (five criteria) and clinical importance of study findings

Evidence Synthesis Primer (Part 2)

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Validity Assessment:	Criteria: Assessment Randomization: Computer randomization stratified by center, age, and severity of respiratory failure Blinding: Open Label (not blinded based on impossibility of making treatment assignment) Baseline Group Comparability: Groups were comparable based on review of Table 1 Follow up: Survival curves indicate patients were followed up to 90 days after surgery. Four patients our of 205 randomized were excluded from analysis (2%). Intent to Treat: Analyses were performed in the intention to treat population, defined as all patients who underwent randomization minus exclusions.
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- Sample Size and Power
- Randomization
- Blinding
- Baseline Group Comparability
- Follow-Up
- Intent to Treat

Career Development Series 2021

Sample Size & Power

Statistical Power

- Definition: The ability to detect differences in groups (effect) if a difference exists.

Sample Size & Power

	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	
Sampling Indicates No Group Differences		

If group differences exist and our sampling evidence says so, we are correct.

Sample Size & Power

	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	
Sampling Indicates No Group Differences		Correct

If group differences do not exist and our sampling evidence says so, we are correct.

Sample Size & Power

	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	Type I Error (α)
Sampling Indicates No Group Differences		Correct

If sampling tells us group differences exist but in truth they do not, we have made an error.

Sample Size & Power

	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	Type I Error (α)
Sampling Indicates No Group Differences	Type II Error (β)	Correct

If sampling tells us no group differences exist but in truth they do, we have made an error.

Sample Size & Power

	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	Type I Error (α)
Sampling Indicates No Group Differences	Type II Error (β)	Correct

Complete framework for how sampling evidence relates to unknown truth.

Sample Size & Power

	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	Type I Error (α)
Sampling Indicates No Group Differences	Type II Error (β)	Correct

Focus now on the truth – that group differences in fact exist.

Sample Size & Power

	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct	Type I Error (α)
Sampling Indicates No Group Differences	Type II Error (β)	Correct

Group differences exist, but our sampling evidence tells us group differences do not exist. The probability of a type II error is denoted by β.

Sample Size & Power

$(1-\beta) + (\beta) = 1$

	Truth – Yes Group Differences	Truth – No Group Differences
Sampling Indicates Group Differences	Correct (1-β)	Type I Error (α)
Sampling Indicates No Group Differences	Type II Error (β)	Correct

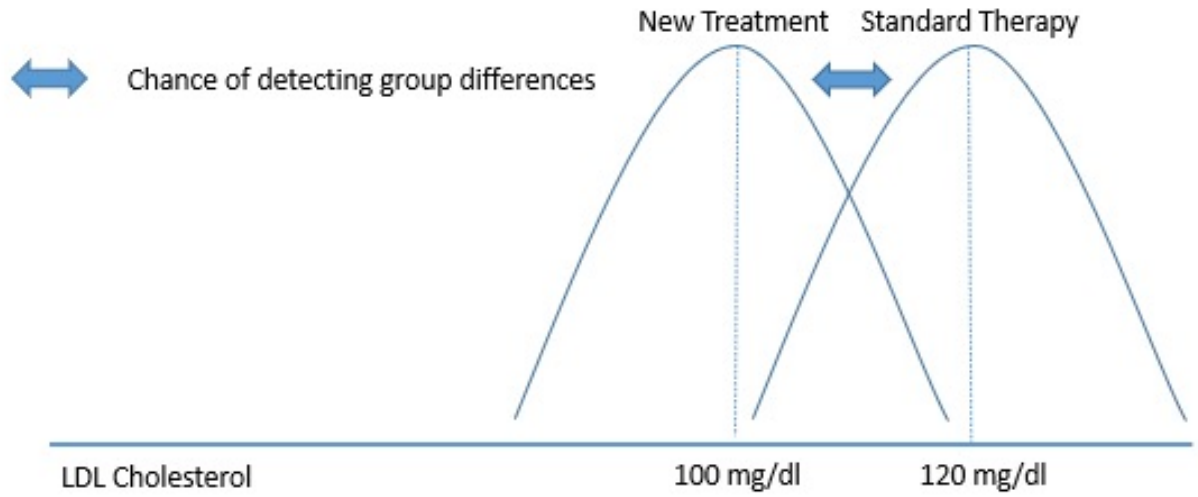
Group differences exist, and our sampling evidence tells us group differences do exist.
The probability of correctly identifying group differences if they exist is 1-β.

What Influences Power?

- Power is the ability to detect group differences (effect), if differences exist
- So, what influences power?

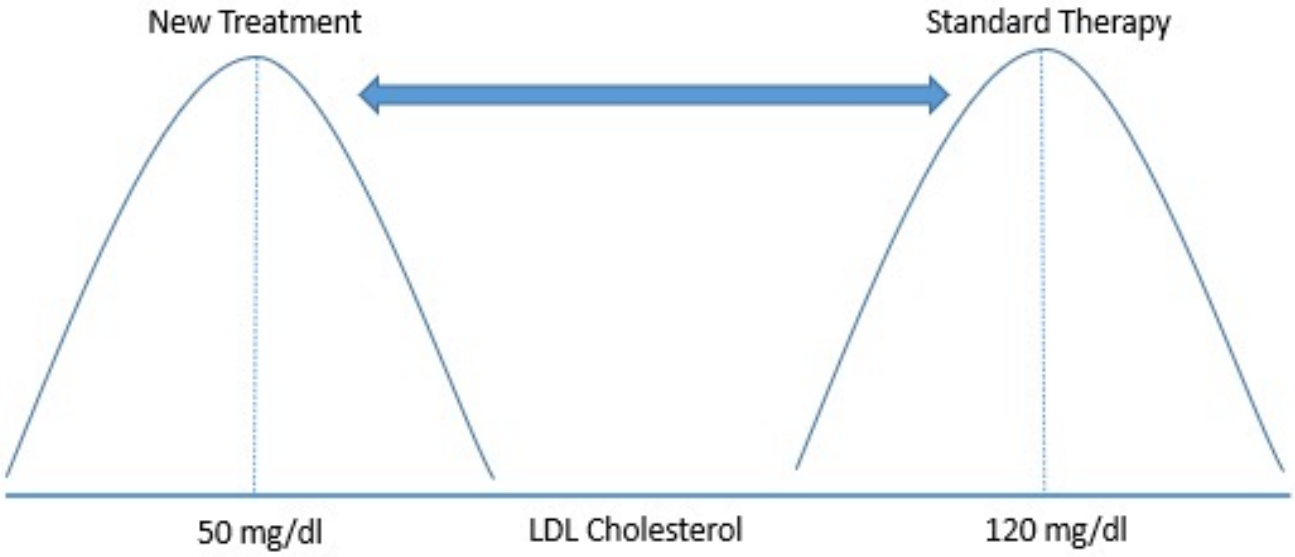
Sample Size & Power

What Influences Power?



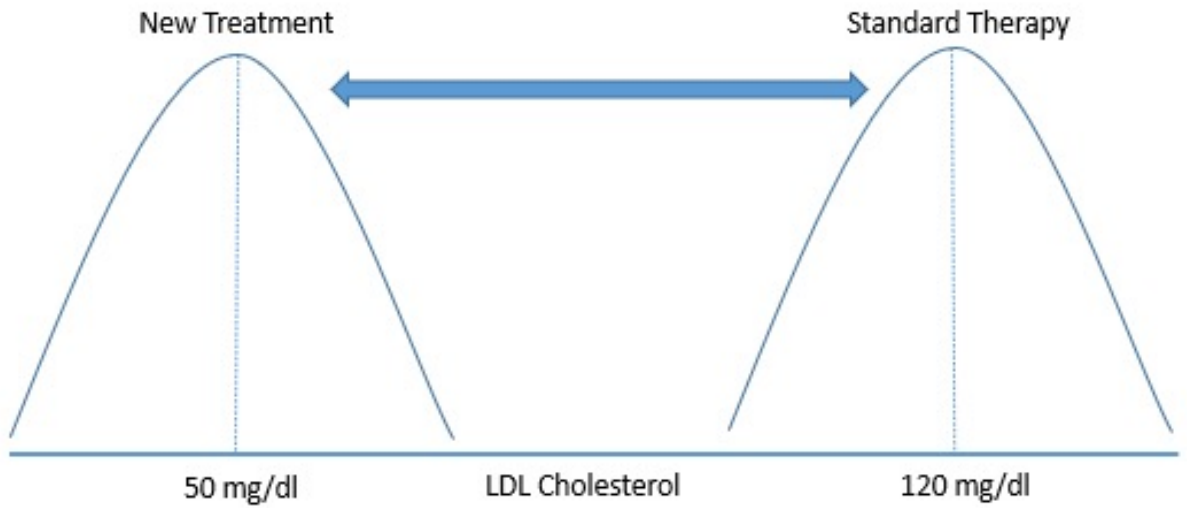
Sample Size & Power

What Influences Power?



Sample Size & Power

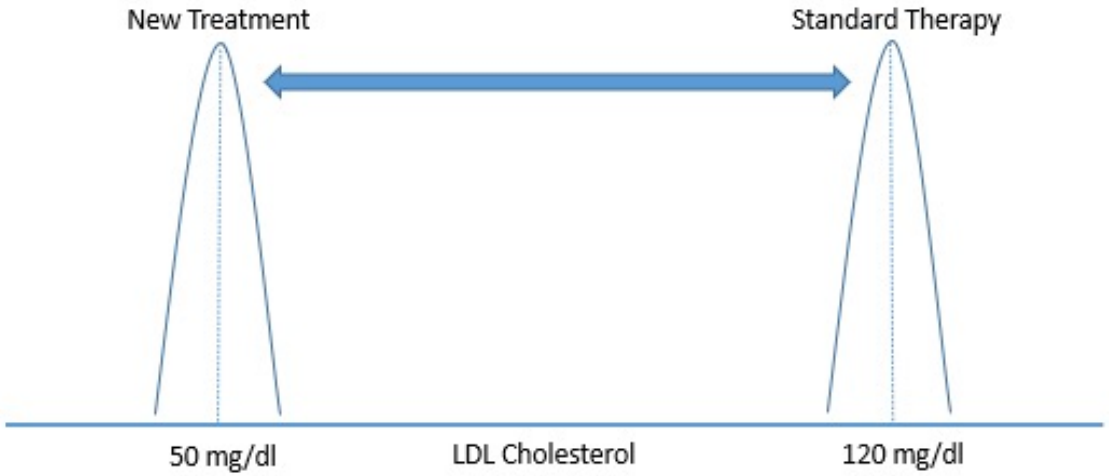
What Influences Power?



Power (the ability to detect true group differences) increases when the effect size (differences between the two groups) increases.

Sample Size & Power

What Influences Power?



Power (the ability to detect true group differences) increases when the variability (standard deviation) of the measured outcome decreases.

What Influences Power?

- Power is the ability to detect group differences (effect), if differences exist
- So, what influences power?
  - Power increases when effect size increases
  - Power increases when variability decreases

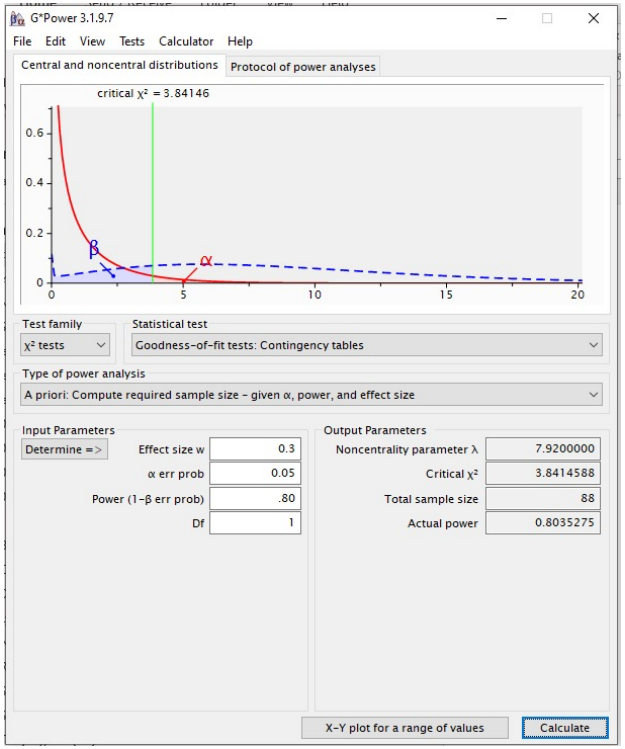
What Influences Power?

- Power is the ability to detect group differences (effect), if differences exist
- So, what influences power?
  - Perhaps most intuitive – the more we know, the greater the probability of detecting true group differences.
  - We know more about a population by increasing the sample size!

What Influences Power?

- Power is the ability to detect group differences (effect), if differences exist
- So, what influences power?
  - Power increases when effect size increases
  - Power increases when variability decreases
  - Power increases as sample size increases

Sample Size & Power



- G*Power (https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower)
- Chi-Square Analysis
- Effect Size (Moderate)
- Alpha = 0.05
- Beta = 0.20
- DF = 1

Career Development Series 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome

Loic Barrot, M.D., Pierre Asfar, M.D., Ph.D., Frederic Mauny, M.D., Ph.D., Hadrien Winiszewski, M.D., Florent Montini, M.D., Julio Badie, M.D., Jean-Pierre Quenot, M.D., Ph.D., Sebastien Pili-Floury, M.D., Ph.D., Belaid Bouhemad, M.D., Ph.D., Guillaume Louis, M.D., Bertrand Souweine, M.D., Ph.D., Olivier Collange, M.D., Ph.D., Julien Pottecher, M.D., Ph.D., Bruno Levy, M.D., Ph.D., Marc Puyraveau, M.Sc., Lucie Vettoretti, Ph.D., Jean-Michel Constantin, M.D., Ph.D., and Gilles Capellier, M.D., Ph.D., for the LOCO$_2$ Investigators and REVA Research Network*

BACKGROUND

In patients with acute respiratory distress syndrome (ARDS), the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network recommends a target partial pressure of arterial oxygen (Pao_2) between 55 and 80 mm Hg. Prospective validation of this range in patients with ARDS is lacking. We hypothesized that targeting the lower limit of this range would improve outcomes in patients with ARDS.

METHODS

In this multicenter, randomized trial, we assigned patients with ARDS to receive either conservative oxygen therapy (target Pao_2, 55 to 70 mm Hg; oxygen saturation as measured by pulse oximetry [Spo_2], 88 to 92%) or liberal oxygen therapy (target Pao_2, 90 to 105 mm Hg; Spo_2, ≥96%) for 7 days. The same mechanical-ventilation strategies were used in both groups. The primary outcome was death from any cause at 28 days.

RESULTS

After the enrollment of 205 patients, the trial was prematurely stopped by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups in the primary outcome. Four patients who did not meet the eligibility criteria were excluded. At day 28, a total of 34 of 99 patients (34.3%) in the conservative-oxygen group and 27 of 102 patients (26.5%) in the liberal-oxygen group had died (difference, 7.8 percentage points; 95% confidence interval [CI], −4.8 to 20.6). At day 90, 44.4% of the patients in the conservative-oxygen group and 30.4% of the patients in the liberal-oxygen group had died (difference, 14.0 percentage points; 95% CI, 0.7 to 27.2). Five mesenteric ischemic events occurred in the conservative-oxygen group.

CONCLUSIONS

Among patients with ARDS, early exposure to a conservative-oxygenation strategy with a Pao_2 between 55 and 70 mm Hg did not increase survival at 28 days. (Funded by the French Ministry of Health; LOCO$_2$ ClinicalTrials.gov number, NCT02713451.)

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Power & Sample Size

Randomization

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*A complete list of investigators in the LOCO$_2$ trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2020;382:999-1008.
DOI: 10.1056/NEJMoa1916431

- Search for the term 'power'
- Methods – Statistical Analysis
  - We performed a power calculation with the published results of two available prospective trials on oxygen targets in ICU populations.
  - We determined that the inclusion of 850 patients would provide a power of 90% to show an absolute between-group difference of 9 percentage points in the primary outcome, assuming a death rate of 30% at day 28 in the liberal-oxygen group, a one-sided test, and a significance level of 0.05.

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Randomization

Randomization

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- Search for the term 'random'
- Trial Procedures
  - Randomization was stratified according to center, age, and severity of respiratory failure according to PaO2:FiO2, with a PEEP of 5 cm of water and a FiO2 of 60 to 100%. Computer randomization was performed in blocks of four.

Blinding

Blinding

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- Search for the term 'blind' or 'conceal'
- Trial Procedures
  - This was an open-label trail because of the impossibility of masking treatment assignments with the use of SpO2 and PaO2 monitoring in the ICU.

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Baseline Group Comparability

Baseline Group Comparability

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Conservative Oxygen (N=99)	Liberal Oxygen (N=102)
Age — yr	63.0±15.5	63.5±14.5
Male sex — no. (%)	65 (65.7)	64 (62.7)
BMI†	27.9±7.2	27.9±6.6
Tidal volume — ml/kg of predicted body weight‡	6.0±0.3	6.2±0.5
Minute ventilation — liters/min	9.4±2.1	9.6±2.1
PEEP — cm of water	6.2±2.7	6.4±3.5
Plateau pressure — cm of water	19.8±5.1	20.8±4.8
Respiratory-system compliance — ml/cm of water	31.1±11.86	28.6±8.99
Pao_2:FIo_2 — mm Hg§	116.8±47.4	120.1±53.6
Pao_2 — mm Hg	90.3±38.8	92.3±44.8
FIo_2 (%)	80.3±18.4	80.1±19.2
Use of catecholamines — no. (%)	70 (70.7)	73 (71.6)
Arterial pH	7.31±0.11	7.31±0.1
Lactate level — mmol/liter	2.2±1.4	2.6±2.2
Hemoglobin level — g/liter	113±25	118±24
SAPS III¶	66.9±13.7	67.9±14.4
SOFA score‖	9.3±3.68	8.9±3.6
Main cause of ARDS		
Pulmonary	78 (78.8)	74 (72.5)
Extrapulmonary	21 (21.2)	28 (27.5)

- Review Table 1
- How well are study participants matched between the conservative and liberal oxygen groups?

Follow-Up

Follow-up

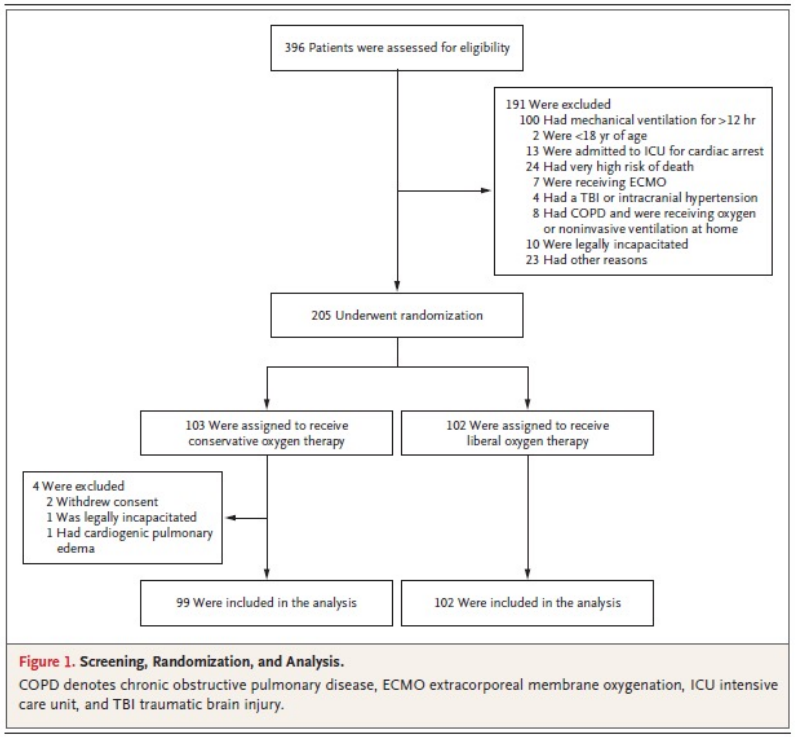

Figure 1. Screening, Randomization, and Analysis.
COPD denotes chronic obstructive pulmonary disease, ECMO extracorporeal membrane oxygenation, ICU intensive care unit, and TBI traumatic brain injury.

- Review Figure 1
- Were patients followed long enough for the outcome to occur?
- Did 80% of patients enrolled in the trial complete the trial?

Intent to Treat

Intent to Treat

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome

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ABSTRACT

BACKGROUND
In patients with acute respiratory distress syndrome (ARDS), the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network recommends a target partial pressure of arterial oxygen (Pao_2) between 55 and 80 mm Hg. Prospective validation of this range in patients with ARDS is lacking. We hypothesized that targeting the lower limit of this range would improve outcomes in patients with ARDS.

METHODS
In this multicenter, randomized trial, we assigned patients with ARDS to receive either conservative oxygen therapy (target Pao_2, 55 to 70 mm Hg; oxygen saturation as measured by pulse oximetry [Spo_2], 88 to 92%) or liberal oxygen therapy (target Pao_2, 90 to 105 mm Hg; Spo_2, ≥96%) for 7 days. The same mechanical-ventilation strategies were used in both groups. The primary outcome was death from any cause at 28 days.

RESULTS
After the enrollment of 205 patients, the trial was prematurely stopped by the data and safety monitoring board because of safety concerns and a low likelihood of a significant difference between the two groups in the primary outcome. Four patients who did not meet the eligibility criteria were excluded. At day 28, a total of 34 of 99 patients (34.3%) in the conservative-oxygen group and 27 of 102 patients (26.5%) in the liberal-oxygen group had died (difference, 7.8 percentage points; 95% confidence interval [CI], −4.8 to 20.6). At day 90, 44.4% of the patients in the conservative-oxygen group and 30.4% of the patients in the liberal-oxygen group had died (difference, 14.0 percentage points; 95% CI, 0.7 to 27.2). Five mesenteric ischemic events occurred in the conservative-oxygen group.

CONCLUSIONS
Among patients with ARDS, early exposure to a conservative-oxygenation strategy with a Pao_2 between 55 and 70 mm Hg did not increase survival at 28 days. (Funded by the French Ministry of Health; LOCO$_2$ ClinicalTrials.gov number, NCT02713451.)

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*A complete list of investigators in the LOCO$_2$ trial is provided in the Supplementary Appendix, available at NEJM.org.

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- Search for the term 'intent'
- Methods – Statistical Analysis
  - Analyses were performed in the intention-to-treat population, defined as all patients who underwent randomization except those who did not provide consent, those for whom the family declined inclusion, and those who did not meet the inclusion criteria as defined in the protocol.

Evidence Synthesis Primer (Part 2)

Reviewer Name:	Answer Key
Review Date:	05/21/2020
PMID:	32160661 (Barrot)
Journal Article Title:	Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. (2020)
Clinical Question:	Among patients with acute respiratory distress syndrome (ARDS) does conservative vs. liberal oxygen therapy improve all-cause mortality at 28 days.
Clinical Question Type:	☒ Treatment ☐ Diagnosis ☐ Prognosis ☐ Systematic Review/Meta-Analysis
Study Design:	Prospective, randomized open label study.
Sample Size and Power:	850 patients 90% between group a priori power analysis based on an expected effect size of 9% from published results of two prospective trials 396 were eligible, 191 were excluded: 205 randomized Trial stopped by the DSMB for increased adverse risk in the conservative oxygenation group.
Validity Assessment:	Criteria: Assessment Randomization: Computer randomization stratified by center, age, and severity of respiratory failure Blinding: Open Label (not blinded based on impossibility of making treatment assignment) Baseline Group Comparability: Groups were comparable based on review of Table 1 Follow up: Survival curves indicate patients were followed up to 90 days after surgery. Four patients our of 205 randomized were excluded from analysis (2%). Intent to Treat: Analyses were performed in the intention to treat population, defined as all patients who underwent randomization minus exclusions.
Validity Summary:	After examining randomization, baseline group comparability, follow up and intent to treat, this study was determined valid for informing practice. While the study was not blinded, the open label nature of this experiment did not likely change study outcomes.

- Sample Size and Power
- Randomization
- Blinding
- Baseline Group Comparability
- Follow-Up
- Intent to Treat

Questions?

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Thank You!

Open for Questions

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Feedback Survey

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