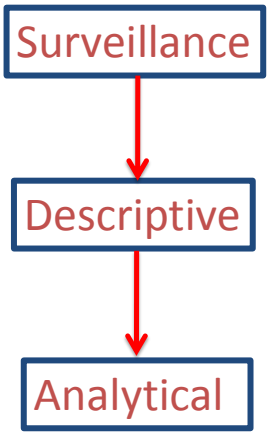
Study Sequence



Study Design

Descriptive

Case reports / Cross-Sectional

- Unable to assess causation
- Describe Disease patterns
- Generate hypotheses

Case-Controlled

- Subjects are selected based on outcome of interest
- Distribution of exposure is based on sample of controls
- Estimates measure of effect, but not directly measures incidence of outcome.
- Controls should represent the sample (not the Cases)

Study Design

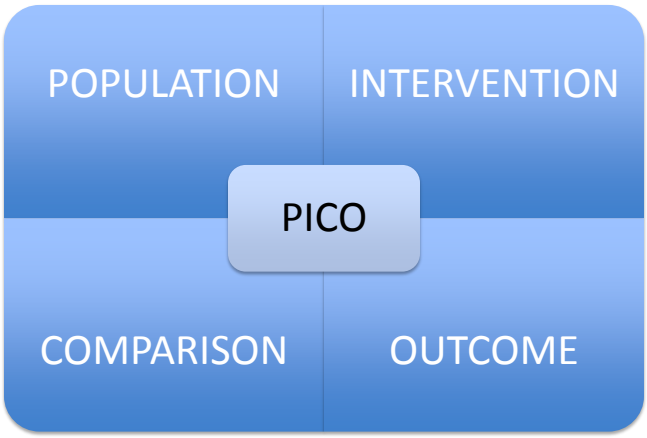
Cohort

- Observational study where exposure (intervention) is not randomly assigned
- Must account for all crucial differences between groups
  - Identify confounders
- Direct measure/compare incidence of outcome between groups
- Requires large population for long periods of time

Randomized Trial

- Subjects are allocated randomly to receive or not receive specific intervention
- "Most Rigorous"
  - Groups treated identical except for intervention
  - Controls for all potential biases
- ?External Validity ?

Study Purpose



Population

- Is population similar to my patient
  - Age / BMI / Impairment or Dysfunction level / Acuity level / Comorbidities
- Inclusion/Exclusion Criteria
- Review purpose

- Karachalios et al, JBJS, 2005.

Intervention

- Require special training/equipment
- External validity
- Appropriate for population and disease process
  - Clinical reasoning
- Review purpose

- Petterson et al, Arth Rheum, 2009.

Comparison

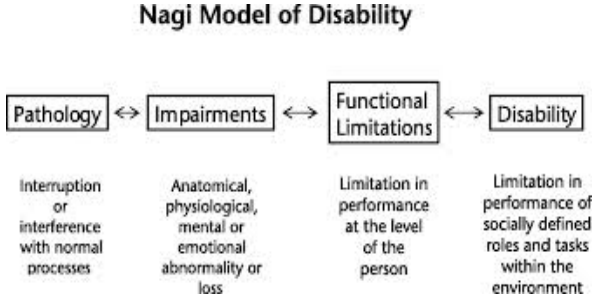
- Appropriate for population
  - Standard of Care
- "Straw Dog"
- Review purpose

- Sherry & Best, JOSPT, 2004

Phase 2*
• *15 min of moderate-intensity stationary biking, moderate level of resistence and moderate work level; should feel some perceived exertion*
• *5 min of moderate-velocity walk*
• *Supine hip flexion with knee extension stretch 4 x 20 sec*
• *Standing hip flexion with knee extension stretch with slow side to side rotation, 4 x 20 sec*
• *Prone leg curls, 3 x 10 reps with ankle weights for resistance*
• *Hip extension in standing with knee straight using Thera-Band resistance, 3 x 10 reps*
• *Non-weight-bearing "foot catches," 3 x 30 sec (Figure 2)*
• *Symptom-free practice without high-speed maneuvers*
• *Ice for 20 min if any symptoms of local fatigue or discomfort are present*

Outcome

- How is outcome defined
- What measures will be used to represent the outcome
- Review the purpose



Quality of Evidence Guidelines

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

STROBE: COHORT STUDY
http://www.strobe-statement.org/

PRISMA: SYSTEMATIC REVIEW/META-ANALYSIS
http://www.prisma-statement.org/

QUADAS-2: DIAGNOSTIC STUDIES
http://www.bris.ac.uk/quadas/

Statistics

Parametric Tests

- Compare means between groups or within groups
- t-test, ANOVA

- Assumptions
  - Normal Distribution of data
  - Equal variability across groups
  - Independence of data

Nonparametric Tests

- Compare medians/distributions of scores
- Kruskal-Wallis test, Mann-Whitney U

- Use when Parametric Assumptions are not met
- Erroneously assumed to be less powerful statistics

Hypothesis testing
"P-Value"

- Statistics test the **NULL** hypothesis that:
  - There is NO difference between group means
- α = Threshold for probability for falsely rejecting the null hypothesis.
  - Traditionally = 0.05
  - Traditionally used to dictate "Statistical Significance"

- Clinically Meaningful?

Fu et al. AJSM 2013

Fu et al: Effect of early whole body vibration therapy on NM control after ACLR
Conventional ACLR vs. WBVT+conventional
Looked at lots of measures
Result: WBVT resulted in significantly better . . . SL hop . . .
Conclusion: WBVT improved . . . . SL HOP

P value Example

Fu et al, AJSM, 2013

	Baseline			3 Months Postoperatively		6 Months Postoperatively		
	Reference	WBVT	*P* Baseline	Reference	WBVT	Reference	WBVT	*P* Overall
Functional tests								
1-legged hop, cm								
RL	105.1 ± 37.2 (89.1-121.0)	100.1 ± 33.2 (84.2-116.1)	.661	—	—	129.5 ± 38.4 (114.5-144.6)	140.8 ± 27.1 (125.8-155.9)	.022[b]

Continuous Data

Hypothesis Testing
"Confidence Intervals"

- Given a desired level of confidence (ie 95%), the confidence interval is a range of values within which the population value is likely to be found.
- Size of the Confidence Interval determined by:
  - Sample Size
  - Variance
- Not statistically significant if:
  - CIs Overlap OR
  - CI of Difference between means include 0
  - Most conservative assessment
- Clinically Meaningful?

CI Example

Fu et al, AJSM, 2013

	Baseline			3 Months Postoperatively		6 Months Postoperatively		
	Reference	WBVT	*P* Baseline	Reference	WBVT	Reference	WBVT	*P* Overall
Functional tests								
1-legged hop, cm								
RL	105.1 ± 37.2	100.1 ± 33.2	.661	—	—	129.5 ± 38.4	140.8 ± 27.1	.022[b]
	(89.1-121.0)	(84.2-116.1)				(114.5-144.6)	(125.8-155.9)	

Effect Size
Cohen's D

- $X_{treatment} - X_{comparison} / SD_{pooled}$
- Treatment effect relative to variability of the measure
  - < 0.2 : Trivial
  - 0.2-0.5 : Small
  - 0.5-0.8 : Moderate
  - > 0.8 : Large
- Also has CI
- Clinically Meaningful?

Effect Size Example

Fu et al, AJSM, 2013

	Baseline			3 Months Postoperatively		6 Months Postoperatively		
	Reference	WBVT	*P* Baseline	Reference	WBVT	Reference	WBVT	*P* Overall
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Effect Size = 0.34 95%CI (-0.41, 1.09)

Responsiveness

- Sensitivity to detect change when a patient's status changes between time points
- Indicates magnitude of intervention related changes
  - For evaluation studies: Must detect "clinically meaningful" changes
- Measures may be:
  - Distribution Based – Minimum Detectable Change
  - Anchor Based – Minimal Clinically Important Difference

Responsiveness Measures

Distribution Based MDC	Anchor Based MCID

• Smest "true" change
• Considers sample's characteristics
• No indication of importance of change
• Examples
  • Effect Size/SRM/SEM
	• Smest change perceived as beneficial by pts.
	• No account for precision
	• Varies with baseline
	• Explicit defines minimal importance
	• Examples
	  • ROC / Correlations

MDC Example

Fu et al, AJSM, 2013

	Baseline			3 Months Postoperatively		6 Months Postoperatively		
	Reference	WBVT	*P* Baseline	Reference	WBVT	Reference	WBVT	*P* Overall
Functional tests								
1-legged hop, cm								
RL	105.1 ± 37.2 (89.1-121.0)	100.1 ± 33.2 (84.2-116.1)	.661	—	—	129.5 ± 38.4 (114.5-144.6)	140.8 ± 27.1 (125.8-155.9)	.022[b]

Mean Difference = 11.30 cm 95% CI (-14.5, 37.12)

SEM = 4.52 cm (Bolgla, JOSPT, 1997)

Results Interpretation

- P > 0.05
  - Fail to reject the null: Unable to show that treatment effect occurred OR
  - There is not enough evidence to conclude . . . OR
  - Observed difference in treatment groups may be due to change alone
- P < 0.05
  - There is evidence to suggest that the outcome of treatment A is different that treatment B
- P = X
  - If the null is true, the probability of obtaining a statistic more extreme that the one from this sample = X.

Results Interpretation

- Combine results of traditional Hypothesis test results with Responsiveness results
  - Is MCID/MDC in the 95% CI?
    - If P< α and MCID/MDC < 95% CI, then 95% likely that there is a clinically meaningful treatment benefit
      - "Definitive Trial"
    - If P< α and MCID/MDC within 95% CI and then effect may be trivial
    - If P> α and MCID/MDC > 95% CI, then 95% likely that there is a clinically meaningful treatment benefit
      - "Definitely Negative Trial"
    - If P> α and MCID/MDC within 95% CI, then there may be inadequate statistical power

Fu et al, AJSM, 2013

	Baseline			3 Months Postoperatively		6 Months Postoperatively		
	Reference	WBVT	*P* Baseline	Reference	WBVT	Reference	WBVT	*P* Overall
Functional tests								
1-legged hop, cm								
RL	105.1 ± 37.2 (89.1-121.0)	100.1 ± 33.2 (84.2-116.1)	.661	–	–	129.5 ± 38.4 (114.5-144.6)	140.8 ± 27.1 (125.8-155.9)	.022[b]

Effect Size = 0.34 95%CI (-0.41, 1.09)

Mean Difference = 11.30 cm 95% CI (-14.5, 37.12)

SEM = 4.52 cm (Bolgla, JOSPT, 1997)

Dichotomous Data

Incidence Rate

- The rate of instantaneous change in disease status over time

- IR = $\frac{\text{\# new cases}}{\text{total person-time of observation}}$

Absolute Associations

- Incidence Rate Difference
  - $IRD_{tx} - IRD_{comp}$
- Provides assessment of "real difference"

IR Relative Associations

- Incidence Rate Ratio: Ratio of the incidence rate among the exposed to the incidence rate of the unexposed
- $IRR = IR_{tx} / IR_{comp}$

- Interpretation
  - Those exposed have 3x the rate of outcome as the those who are unexposed

Incidence Rate Example

(Cross, 2013)

	Injuries (n)	(AE) (n)	Injury Rate (per 1000 AEs)	aIRR* (95% CI)
Males				
Competition	139	114,034	1.2	3.01 (2.41, 3.77)
Practice	170	413,460	0.411	
Females				
Competition	71	136,837	0.5	1.67 (1.25, 2.23)
Practice	130	419,721	0.31	

AEs, athlete exposures; aIRR, adjusted incidence rate ratio; CI, Confidence Interval

Risk: (Cumulative Incidence)

- Prospective Data Collection
  - Proportion of fixed population that develops outcome in a stated period of time
  - Risk = $\frac{\text{\# of new cases}}{\text{total population at risk}}$

Myklebust et al, 2003
Example for Risk Stats

Myklebust et al 2003 in Clin J Sports Med: Prevention of ACL inj in female team handball players. Prospective intervention over 3 season
60 team per season: 1 control season and 2 intervention season
3 balance ex with NM control/balance and planting/landing skills
Used Ors
Only statistical difference between those who completed and those who did not complete program among elite division and elite 2nd intervention to baseline and only 1 less injury than 1st intervention year
Conclusion: Is possible to prevent ACLF with specific NM training

Risk Example

Myklebust *et al*	NC ACL Injuries	Females per group
Control	18	942
Intervention (first year only)	10	855

Risk (Control Group) = 18/942 = 0.019 = 1.9%

Risk (Intervention) = 10/855 = 0.012 = 1.2%

Absolute Associations

- Risk Difference "Absolute Risk Reduction"
  - $R_{tx} - R_{comp}$
- Incidence Rate Difference
  - $IRD_{tx} - IRD_{comp}$
- Provides assessment of "real difference"

Risk Example

Myklebust *et al*	NC ACL Injuries	Females per group
Control	18	942
Intervention (first year only)	10	855

Risk (Control Group) = 18/942 = 0.019

Risk (Intervention) = 10/855 = 0.012

Risk Difference = 0.012 – 0.019 = -0.007 or -0.7% 95%CI(-0.018, 0.004)

Relative Associations

- Risk Ratio: Ratio of risk among exposed to the risk among the unexposed
- RR = R_{tx} / R_{comp}

- Interpretation
  - Those exposed have 3x the risk to get outcome as those who are unexposed
  - 1-2 Mild effect; 2-4 Mod effect; >4 Strong effect

Risk Example

Myklebust *et al*	NC ACL Injuries	Females per group
Control	18	942
Intervention (first year only)	10	855

Risk (Control Group) = 18/942 = 0.019

Risk (Intervention) = 10/855 = 0.012

Risk Difference = 0.019 – 0.012 = 0.007 or 0.7% 95%CI (-0.004, 0.018)

Risk Ratio = 0.012 / 0.019 = 0.63 or 63% 95%CI (0.75, 3.52)

Relative Associations

- Relative Risk Reduction: % reduction in risk in exposed compared to unexposed

- $RRR = \frac{(R_{comp} - R_{tx})}{R_{comp}}$

- Interpretation: The exposed have a ____% (increase or decrease) in risk than the control

Risk Example

Myklebust *et al*	NC ACL Injuries	Females per group
Control	18	942
Intervention (first year only)	10	855

Risk (Control Group) = 18/942 = 0.019

Risk (Intervention) = 10/855 = 0.012

Risk Difference = 0.019 – 0.012 = 0.007 or 0.7%

Risk Ratio = 0.012 / 0.019 = 0.63 or 63%

Relative Risk Reduction = 0.019-0.012 / 0.019 = 0.37 or 37% (-0.9, 62.9)

Relative Associations

- Number Needed to Treat: Number of persons treated to prevent one outcome
- NNT = 1 / ($R_{tx} - R_{comp}$)

Risk Example

	NC ACL Injuries	Females per group
Myklebust *et al*		
Control	18	942
Intervention (first year only)	10	855

Risk (Control Group) = 18/942 = 0.019

Risk (Intervention) = 10/855 = 0.012

Risk Difference = 0.019 – 0.012 = 0.007 or 0.7% 95% CI (-0.004, 0.018)

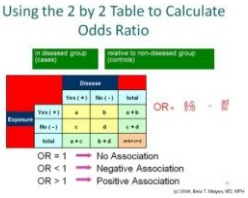
Risk Ratio = 0.012 / 0.019 = 0.63 95%CI (0.75, 3.52)

Relative Risk Reduction = 0.019-0.012 / 0.019 = 0.37 or 37% (-0.9, 62.9)

NNT = 1 /0.007 = 143 95% CI (53 NNTB to ∞ to 255 NNTH)

Relative Associations

- Odds Ratio: Ratio of the odds of exposure among those with the outcome to the odds of exposure among those without the outcome
- OR = ad / bc
- Interpretation
  - Those with outcome are "3x" as likely to have exposure as those without the outcome (controls)
  - Always overestimate the effect
    - Negligible with low risk/prevalence of outcome



OR example

Chan, Skeletal Radio, 2008

Table 2 Results of polytomous logistic regression analysis of risk factors for medial tibiofemoral joint space narrowing (JSN), presented with odds ratio (95% confidence interval), with grade 1 JSN as the reference group

	Grade 2 JSN	Grade 3 JSN
Sex (men referent)	1.91 (0.44–8.35)	0.78 (0.19–3.17)
Age	0.94 (0.86–1.02)	0.94 (0.86–1.03)
BMI[†]	1.04 (0.90–1.20)	1.07 (0.93–1.24)
Duration of knee pain[a]	1.21 (0.99–1.48)	1.25 (1.01–1.53)*
Meniscal tear	6.00 (1.29–27.96)*	2.36 (0.61–9.16)
ACL rupture	0.94 (0.30–2.99)	0.94 (0.30–2.99)

BMI Body mass index, *ACL* anterior cruciate ligament
*$P<0.05$ (pain, $P=0.036$; meniscal tear, $P=0.023$)
[a] Incomplete data were estimated.

Interpretation

- Absolute Associations
  - > 0 = Causative
  - < 0 = Protective
- Relative Associations
  - <1: Protective
  - >1: Causative
  - =1: No effect
  -

Rate Ratio ↑	Rate Ratio ↓	Strength of Assoc
1.0-1.2	0.9-1.0	None
1.2-1.5	0.7-0.9	Weak
> 1.5	< 0.7	Mod to Strong

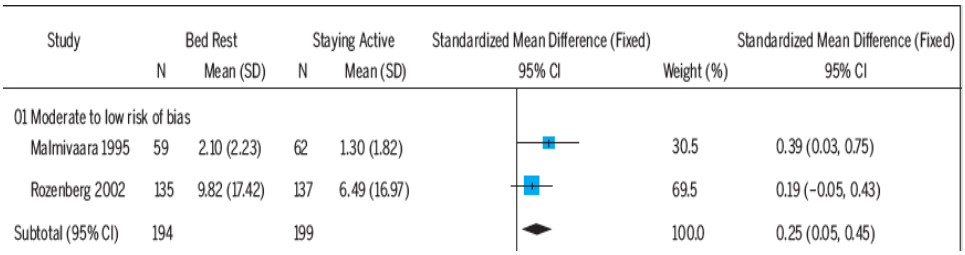
(Monson, 1990)

- Confidence Intervals should be provided

Systematic Review

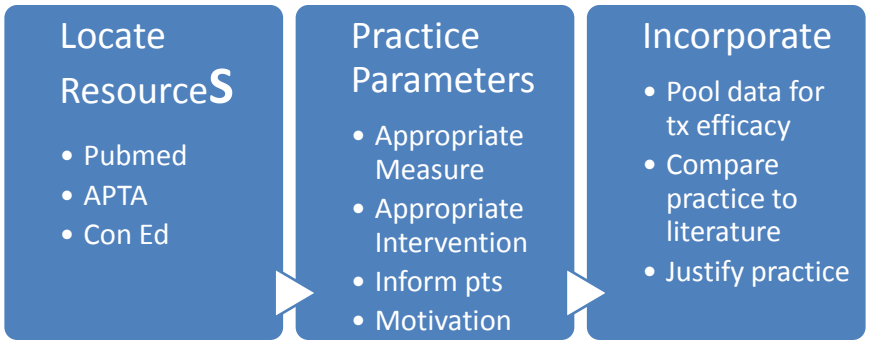
Data Pooling

- Overall Increase in N
  - Increased ability to detect significant treatment effect
  - Enhanced precision of measurements
- Must make sure that data is comparable



Application to Practice

Incorporation into Clinical Practice



Barriers to Integration