Therapy Articles

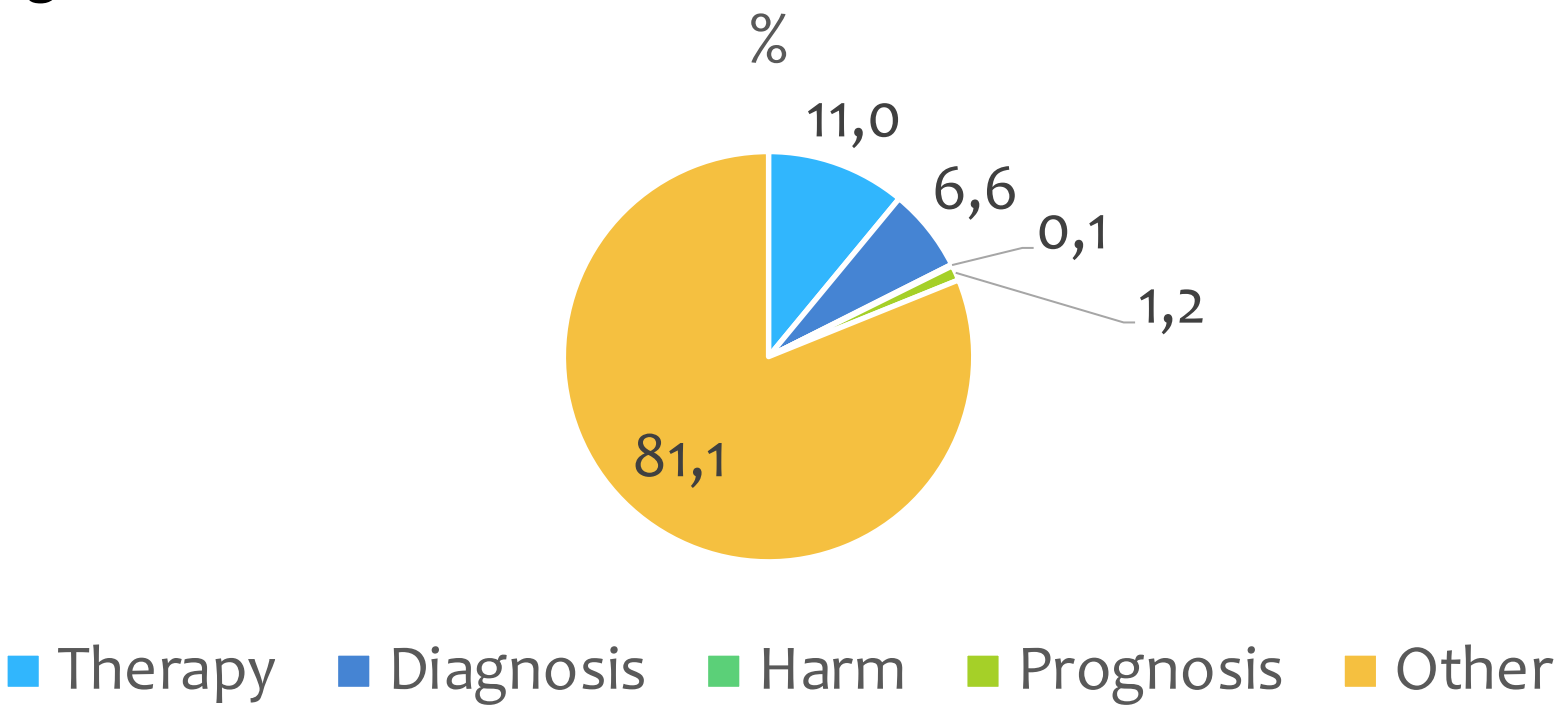
https://pixabay.com/vectors/capsule-pills-medicine-158568/

Objectives

* This presentation aims to present details used to appraise scientific evidence of therapy articles.
* At the end of this session, the participants are expected to;
  * Discuss the significance of therapy, diagnosis, harm, and prognosis articles in medical literature
  * Discuss the CEBM criteria for critical appraisal
  * Discuss the validity, treatment effect, and applicability of a randomized controlled article on therapy

Number of PubMed articles

* **Keywords in title/abstract:** diabetes, therapy, diagnosis, harm, prognosis



Clinical Scenario

* 60 year old female presents with right low back and leg pain for 6 months, much worse in the last 2 weeks. She wants pain relief.
* Exam: very mild weakness in the right extensor hallucis longus (EHL)
* Impression: Right L5 lumbar radiculopathy

Clinical Question

* *P* In patients with lumbar radiculopathy
* *I* Does lumbar disk surgery
* *C* Compared with non-operative care
* *O* Result in improved pain relief

An Article

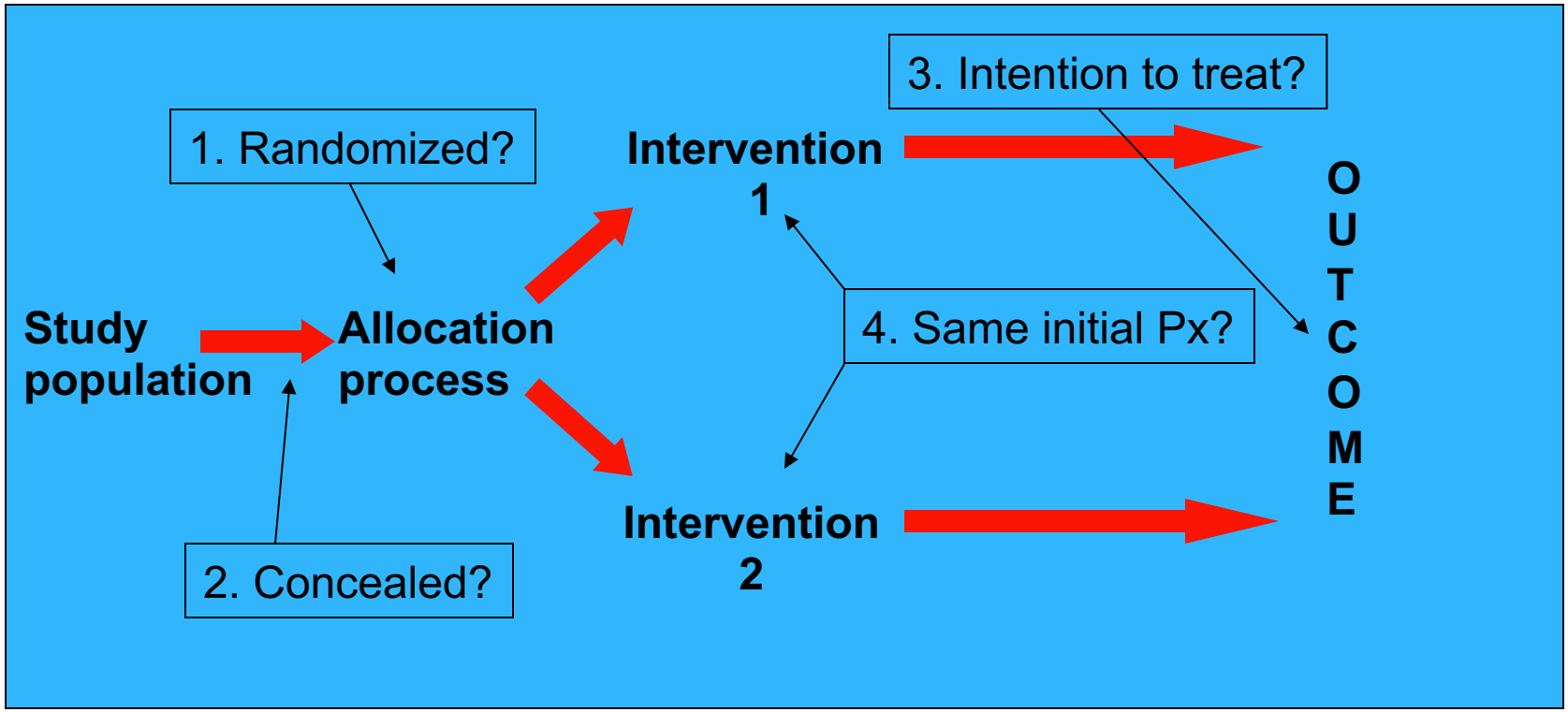
* Weinstein et al., Surgical vs nonoperative treatment for lumbar disk herniation, the Spine Patient Outcomes Research Trial (SPORT): a randomized trial.
* JAMA 2006;296:2441-2550.
* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2553805/

Critical Appraisal

* Does this study address a clearly focused question?
* Did the study use valid methods to address this question?
* Are the valid results of this study important?
* Are these valid, important results applicable to my patient or population?

https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools

Critical Appraisal of Therapy Articles
VALIDITY



Critical Appraisal of Therapy Articles VALIDITY

* Did experimental and control groups begin the experiment with a similar prognosis?
* Were patients randomized?
* Was allocation to groups at the time of randomization concealed?
* Were patients analyzed in the groups to which they were randomized?
* Were patients in the treatment and control groups similar with respect to known prognostic factors?

Why Randomize?

* To balance known and unknown prognostic factors between the treatment arms

SPORT trial

* Methods section:
  * “Computer-generated random treatment assignment based on permuted blocks (randomly generated blocks of 6, 8, 10, and 12) within sites occurred immediately after enrollment via an automated system at each site, …”

Why concealment?

* The individual who enrolls a subject into a trial should not be aware of which arm of the study a patient will be assigned to.
* If allocation not concealed, patients may be systematically enrolled into one arm of the study or the other.
* Can be accomplished by remote randomization, for example.

What is ITT?

* The Intention-To-Treat principle states that research subjects should be analyzed in the group to which they were initially assigned, regardless of what treatment they actually received.
* Treatment decisions are almost always related to prognosis, and those who deviate from a study protocol will have a different prognosis from those who do not.
* ITT preserves the prognostic balance of randomization.

SPORT trial

* Methods:
  * “The analyses for the primary and secondary outcomes used all available data for each period on an intent-to-treat basis.”

Randomization

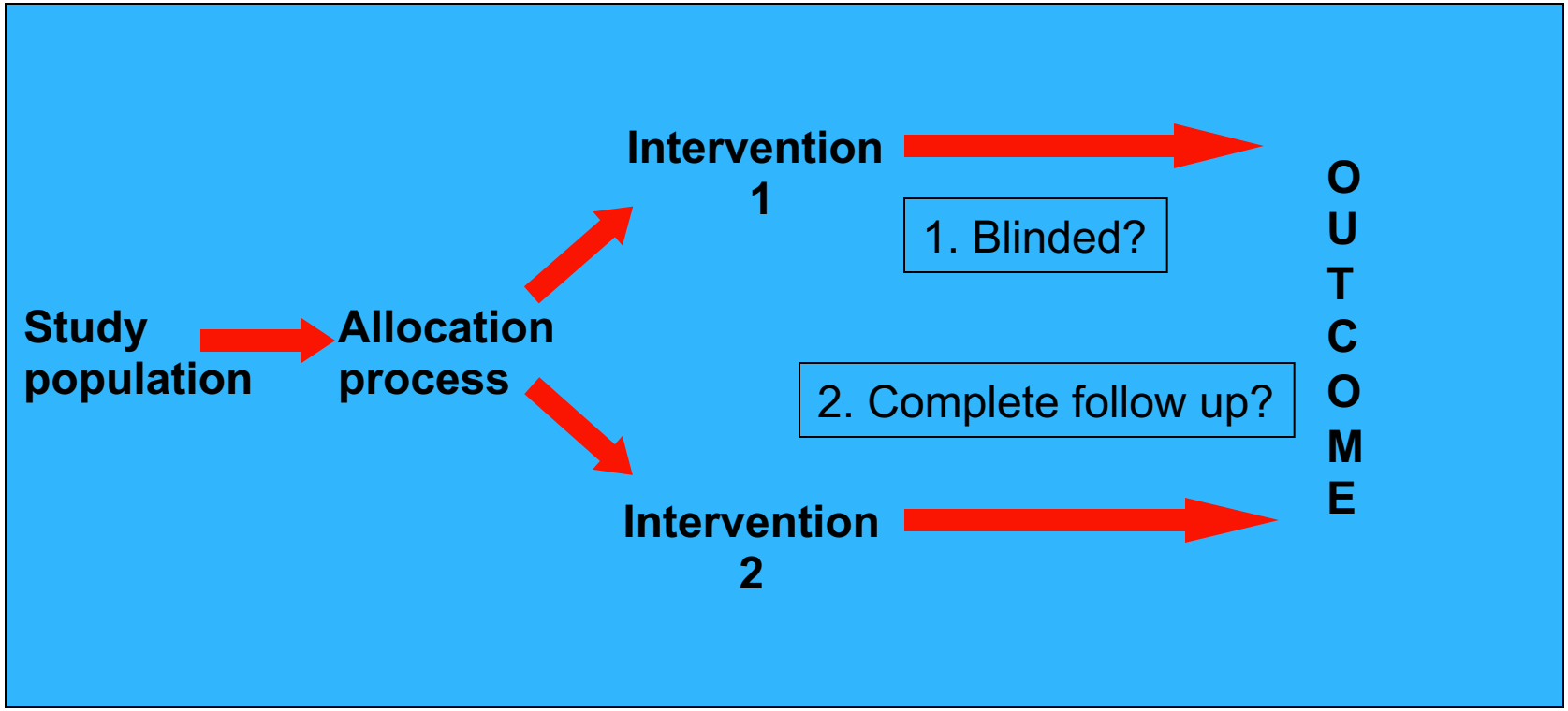
* Either systematic or random errors may subvert the outcome of randomization
* Look for “Table 1” which should describe the baseline demographics, comorbid conditions, and other prognostic variables of study subjects
* Differences between study groups aren’t surprising. Look for the magnitude of difference in important prognostic variables

SPORT trial

* Table 1 of the paper reports baseline characteristics for the randomized arms of the study.

Critical Appraisal of Therapy Articles VALIDITY

* Did experimental and control groups retain a similar prognosis after the experiment started?



Critical Appraisal of Therapy Articles VALIDITY

* Did experimental and control groups retain a similar prognosis after the experiment started?
  * Were patients aware of group allocation?
  * Were clinicians aware of group allocation?
  * Were outcome assessors aware of group allocation?
  * Was follow-up complete?

Blinding
VALIDITY

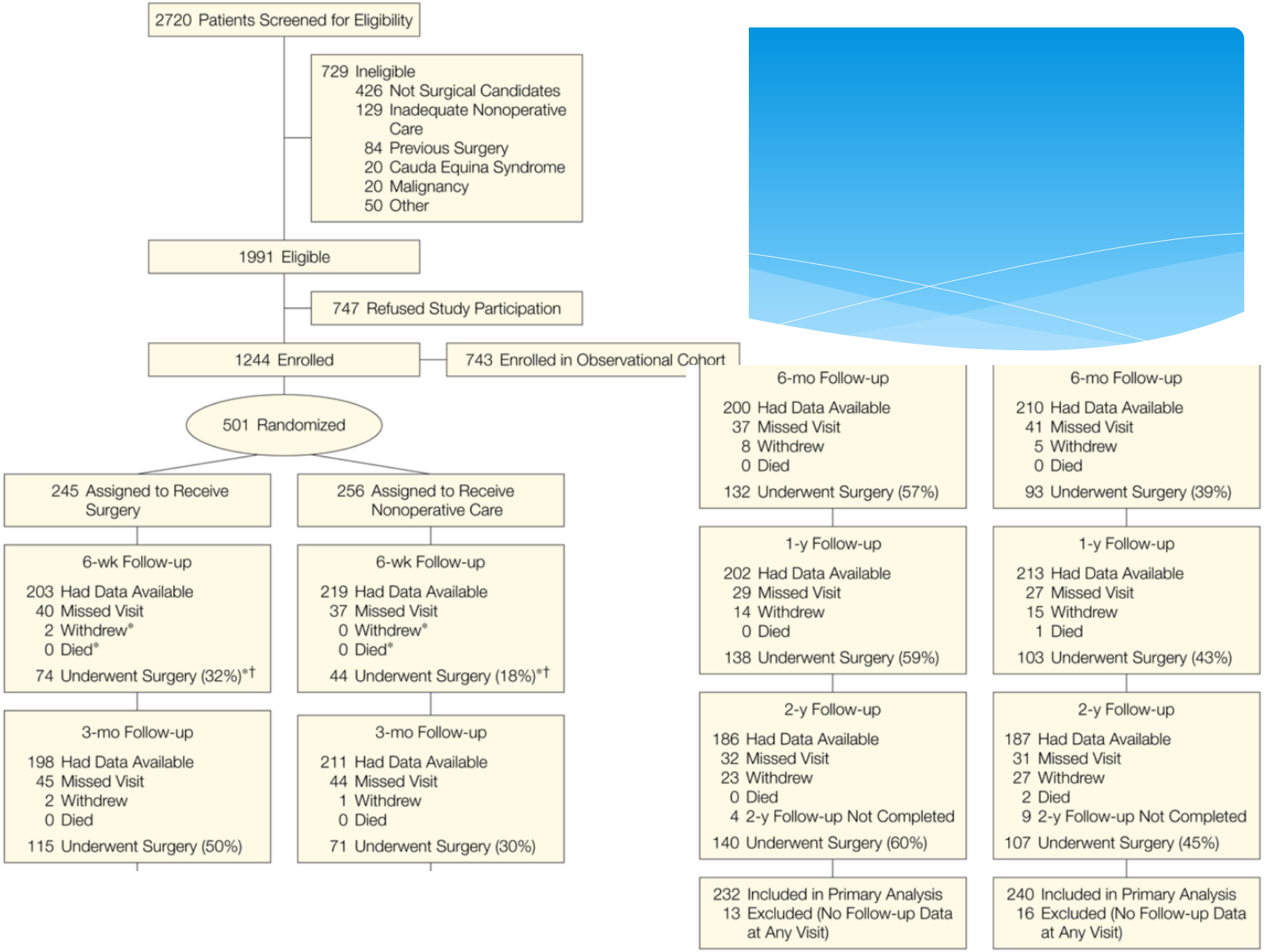
* Despite study design, patients, clinicians, or outcome assessors may be aware of study arm assignment
* Blinding is not always possible or necessary
* Blinding becomes more important when the study outcome involves judgment (e.g., pain) and less important when the outcome is objective and discrete (e.g., all-cause mortality)

Follow Up
VALIDITY

* Status of all study subjects should be accounted for
* Subjects lost to follow up often have a different prognosis (i.e., worse) relative to study endpoints than those accounted for. Look for description of prognosis for patients lost to follow up.
* Rate of study outcome relative to subject loss (worst case scenario)

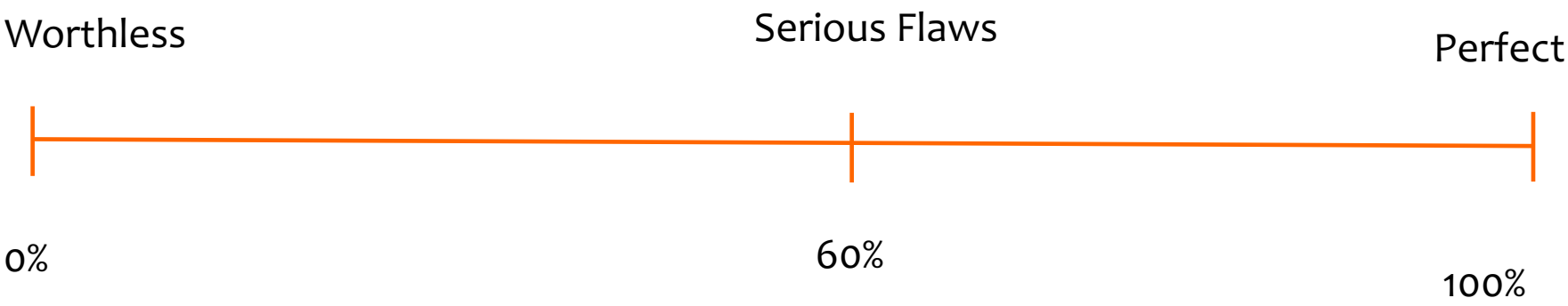
SPORT trial

* Figure 1 displays the flow of patients through the SPORT trial.


2720 Patients Screened for Eligibility
729 Ineligible
426 Not Surgical Candidates
129 Inadequate Nonoperative Care
84 Previous Surgery
20 Cauda Equina Syndrome
20 Malignancy
50 Other
1991 Eligible
747 Refused Study Participation
1244 Enrolled
743 Enrolled in Observational Cohort
501 Randomized
245 Assigned to Receive Surgery
256 Assigned to Receive Nonoperative Care
6-wk Follow-up
203 Had Data Available
40 Missed Visit
2 Withdrew*
0 Died*
74 Underwent Surgery (32%)*†
6-wk Follow-up
219 Had Data Available
37 Missed Visit
0 Withdrew*
0 Died*
44 Underwent Surgery (18%)*†
3-mo Follow-up
198 Had Data Available
45 Missed Visit
2 Withdrew
0 Died
115 Underwent Surgery (50%)
3-mo Follow-up
211 Had Data Available
44 Missed Visit
1 Withdrew
0 Died
71 Underwent Surgery (30%)
6-mo Follow-up
200 Had Data Available
37 Missed Visit
8 Withdrew
0 Died
132 Underwent Surgery (57%)
6-mo Follow-up
210 Had Data Available
41 Missed Visit
5 Withdrew
0 Died
93 Underwent Surgery (39%)
1-y Follow-up
202 Had Data Available
29 Missed Visit
14 Withdrew
0 Died
138 Underwent Surgery (59%)
1-y Follow-up
213 Had Data Available
27 Missed Visit
15 Withdrew
1 Died
103 Underwent Surgery (43%)
2-y Follow-up
186 Had Data Available
32 Missed Visit
23 Withdrew
0 Died
4 2-y Follow-up Not Completed
140 Underwent Surgery (60%)
2-y Follow-up
187 Had Data Available
31 Missed Visit
27 Withdrew
2 Died
9 2-y Follow-up Not Completed
107 Underwent Surgery (45%)
232 Included in Primary Analysis
13 Excluded (No Follow-up Data at Any Visit)
240 Included in Primary Analysis
16 Excluded (No Follow-up Data at Any Visit)

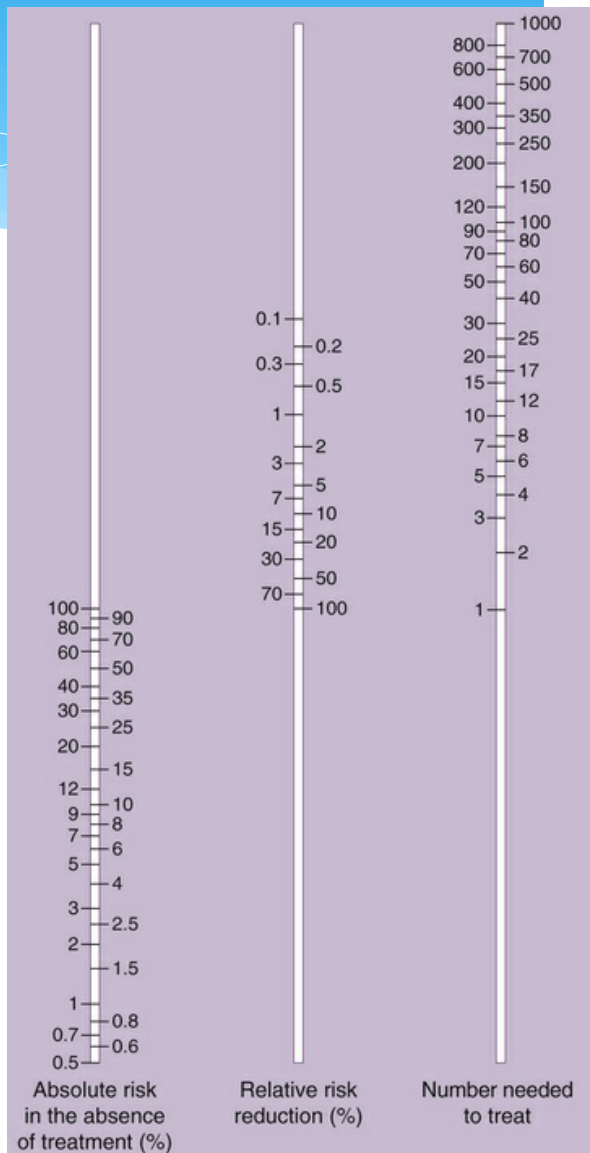
Critical Appraisal of Therapy Articles VALIDITY

* Validity should be seen as an array from 0 to 100%



How large was the treatment effect?

* How precise was the estimate of the treatment effect?
* RRR
* ARR
* NNT
* p
* CI
* CER
* EER
* EER/CER



APPLICABILITY

* Were the patients similar to my patient?
* Were all clinically important outcomes considered?
* Are the likely treatment benefits worth the potential harm and costs?

Patient Similarity APPLICABILITY

* Look to the study inclusion & exclusion criteria
* Look to Table 1 for demographic, prognostic, and co-interventions
* Generalizability of a study's conclusions may not always be appropriate

Outcomes APPLICABILITY

* Side effects
* Cost
* Quality of life
* Short term surgical risks
* Survey instruments should be validated

SPORT trial

* Table 3 shows the adverse event results for the SPORT trial.

Table 3

Operative Treatments, Complications, and Events

	No. (%) (n = 243)*
Diskectomy level	
L2-3/L3-4	9 (4)
L4-5	89 (37)
L5-S1	145 (61)
Operation time, mean (SD), min	79.1 (36.3)
Blood loss, mean (SD), mL	64.7 (88.4)
Blood replacement	4 (2)
Length of stay	
Same day	65 (27)
1 Night	137 (57)
≥2 Nights	37 (15)
Intraoperative complications†	
Dural tear/spinal fluid leak	10 (4)
Vascular injury	1 (0)
Other	2 (1)
None	230 (95)
Postoperative complications/events‡	
Wound infection, superficial	4 (2)
Other	9 (4)
None	226 (95)
Postsurgical reoperation, No. (rate)§	
1 y	
Additional surgery	9 (4)
Recurrent herniation	5 (2)
Complication or other	4 (2)
New condition	0
2 y	
Additional surgery	13 (5)
Recurrent herniation	8 (3)
Complication or other	4 (2)
New condition	0

Balancing Benefit with Harms APPLICABILITY

* The patient's values and preferences must be incorporated into the clinical decision
* Additional harms may not be addressed in a single therapy article

Summary

* What is the significance of therapy, diagnosis, harm, and prognosis articles in medical literature
* How can we apply the CEBM criteria for critical appraisal?
* How can we assess the validity, treatment effect, and applicability of randomized controlled articles on therapy?