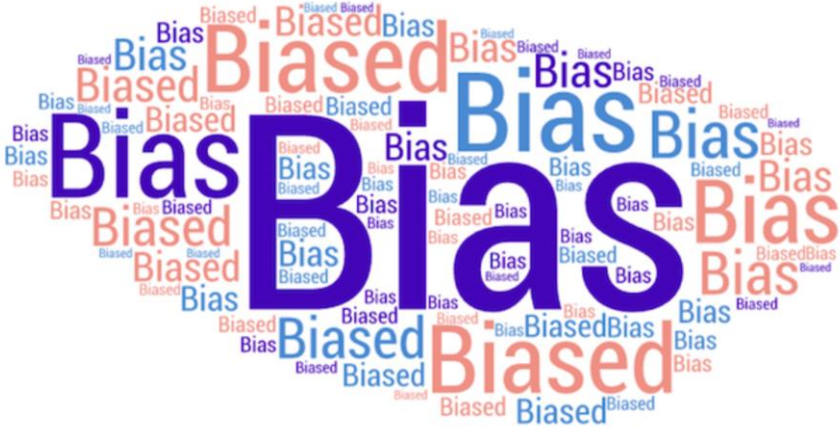
Randomized Controlled Trials
An Overview

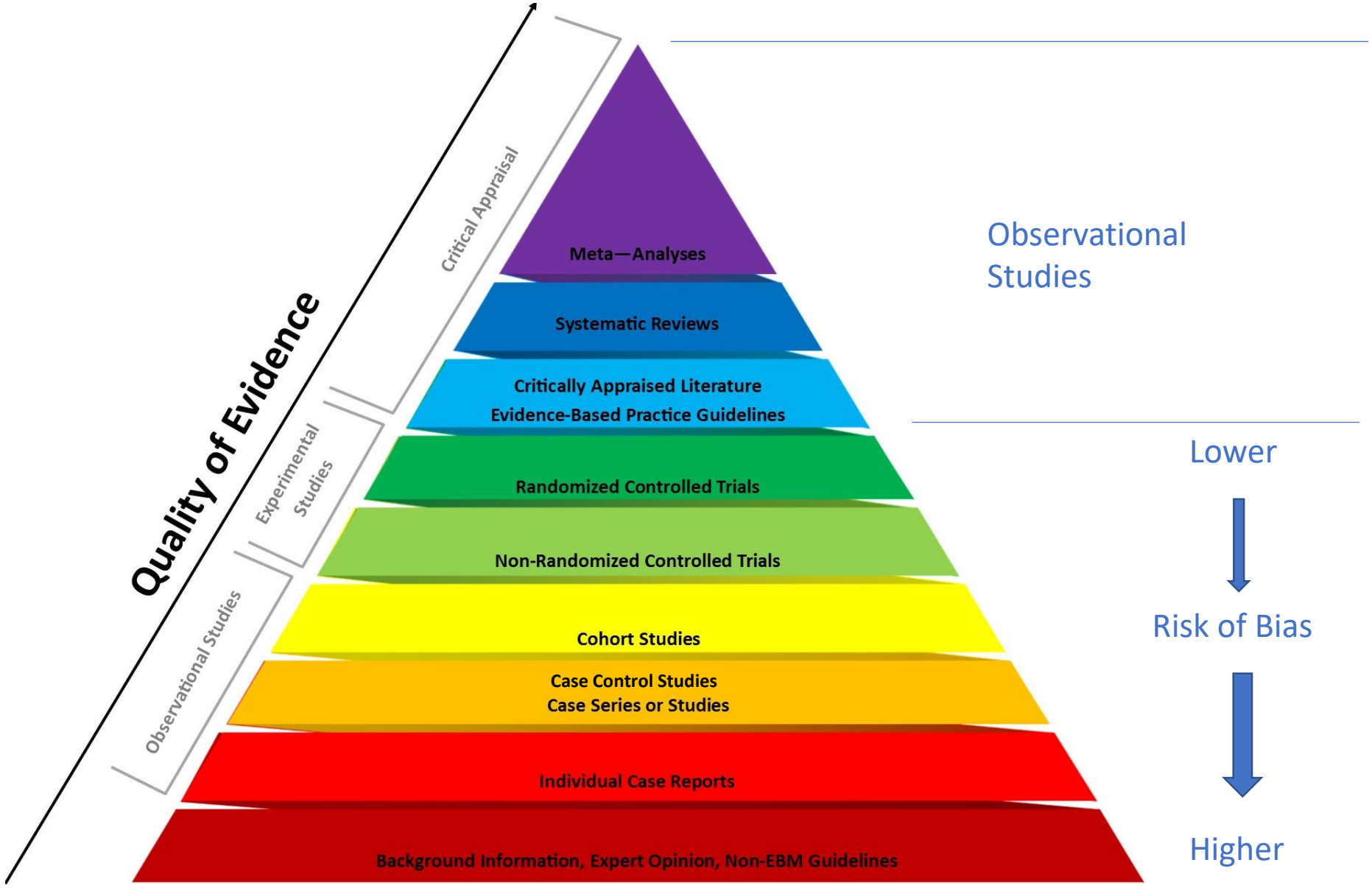
J. M. Fardy, MD, MSc, FRCPC

Randomized Controlled Trials (RCTs)
An Overview



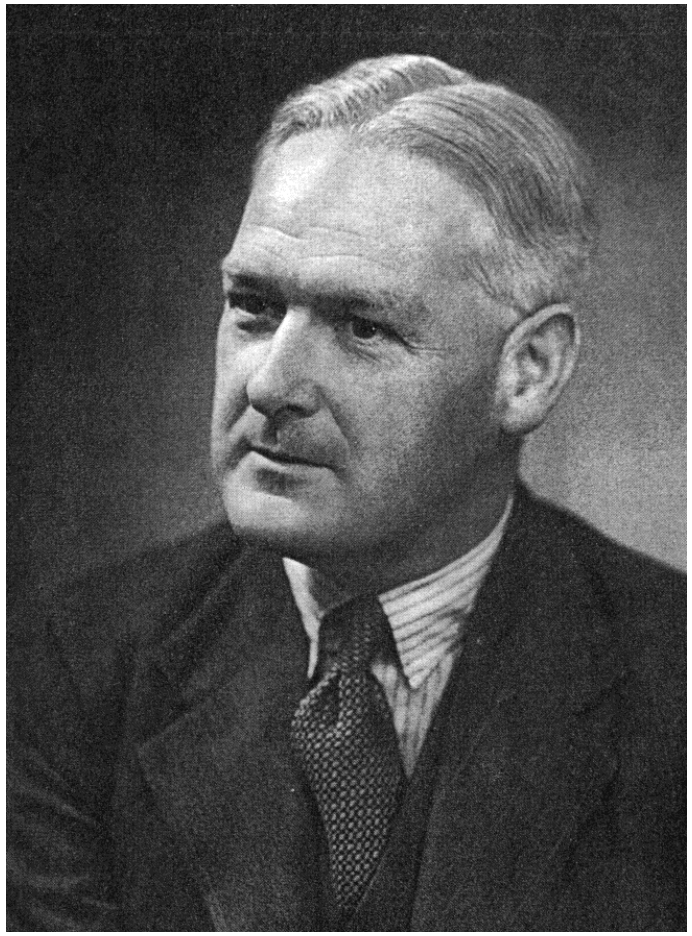
- Review the history of clinical trials
- Focus on the methodology used to minimize bias in RCTs
- Discuss some of the ethical concepts underlying RCTs
- Justify the Intention to Treat analysis of RCT data
- Review the concepts of internal and external validity of RCTs
- Examine the use of real world evidence to improve external validity

Hierarchy of Evidence



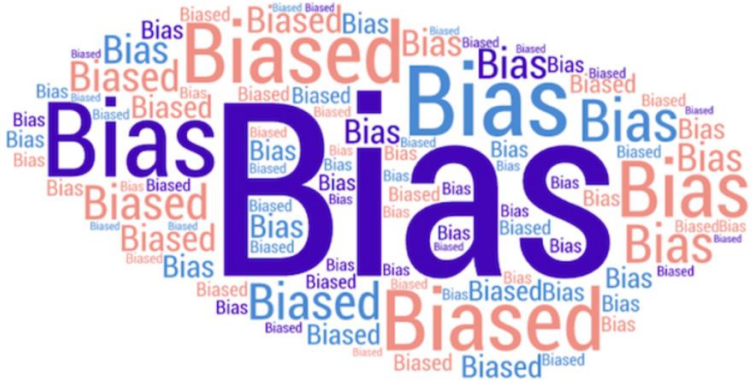
Sir Austin Bradford Hill,1984

- “At its best a trial shows what can be accomplished with a medicine under careful observation and under certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use”



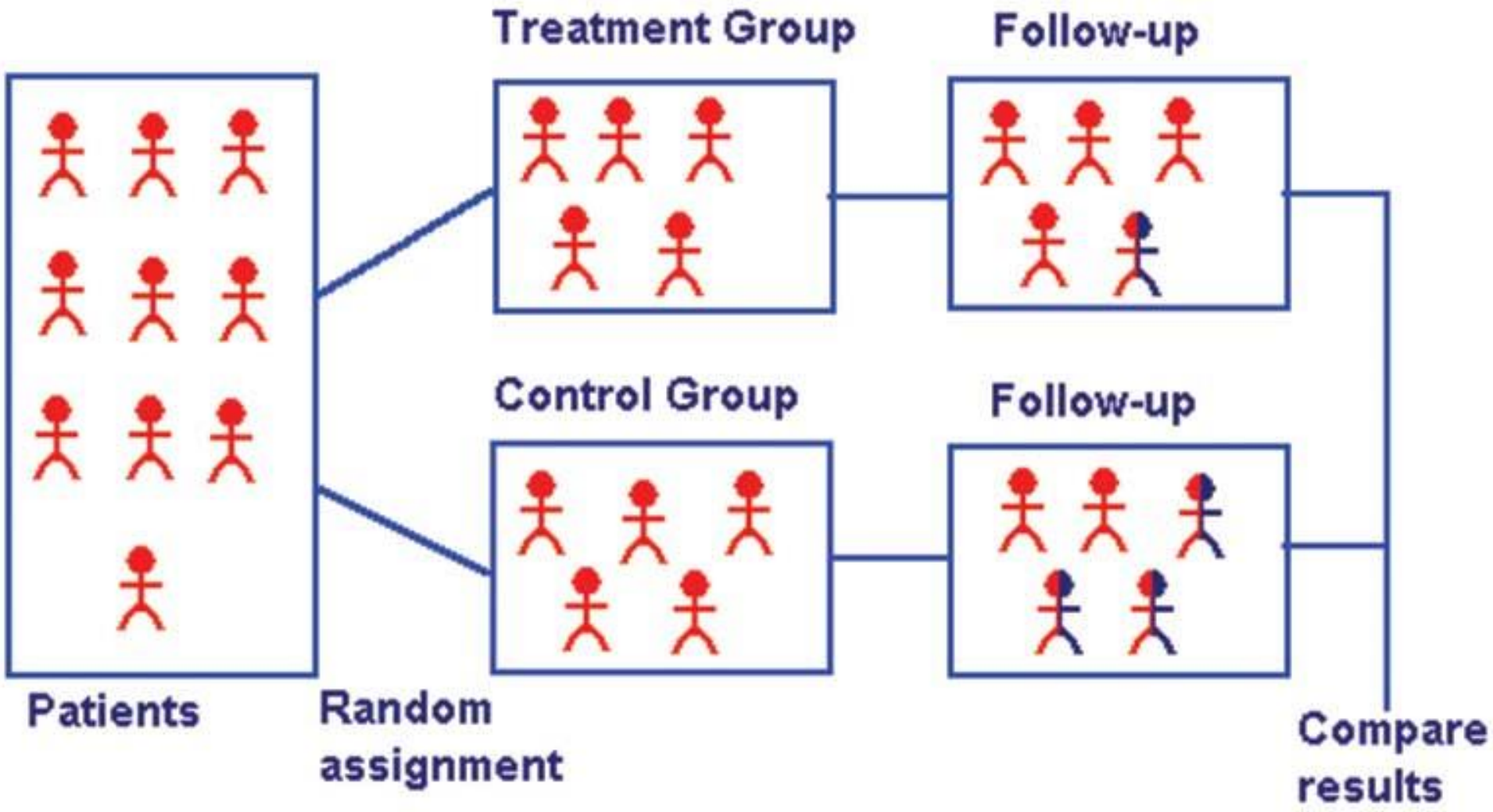
Randomized Controlled Trials (RCTs)

- Scientific experiments designed to test the benefit of drug treatment
- Make use of a variety of techniques to control bias (Evil)
  - Randomization
  - Allocation concealment
  - Controlled treatment
  - Blinding
    - Researchers
    - Patients (Placebo)
    - Outcome assessors
    - Statisticians



Bias: Tendency to favor one group over another

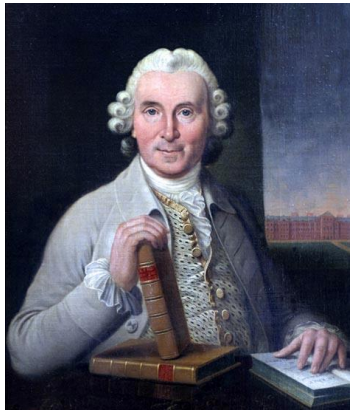
Randomized Controlled Trials (RCTs)



James Lind

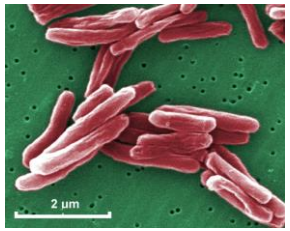
- Born Edinburgh 1716
- On HMS Salisbury in 1747 he allocated 12 men with scurvy
  - Cider
  - Seawater
  - Horseradish, mustard, garlic
  - Nutmeg
  - Elixir Vitriol (H_2SO_4 and EtOH)
  - Oranges and Limes

First Controlled Clinical Trial - 1747



- Selected 12 patients whose "cases were as similar as I could have them" who "lay together in one place" in the fore-hold, all with the same diet
- Two each ordered a daily quart of cyder, 75 drops of elixir vitriol, 6 spoonfuls of vinegar, a course of sea water, an electary suggested by a hospital physician and finally two oranges and one lemon daily.
- The two given citrus fruit improved within days
- Lind hesitated to recommend the therapy because oranges and lemons were too expensive*. It was 50 years before the British navy adopted lemon juice as a compulsory part of seafarer's diet

* Importance of Health Economics



The First Randomized Controlled Trial 1947 Streptomycin for Pulmonary Tuberculosis

- Tuberculosis was endemic in the UK with high morbidity and mortality
- Penicillin of no benefit for TB
- Streptomycin isolated from a fungus
  - Worked in the test tube against TB
  - Worked in guinea pigs with TB
  - Anecdotal evidence it worked in patients
  - Expensive and limited quantity available

- Multicentre controlled trial was planned by the MRC
  - Randomization proposed by Austin Bradford Hill*, a Professor of Medical Statistics at the London School of Hygiene and Tropical Medicine

*Case Control Study of Smoking in Lung Ca / Hill criteria for causation

The First Randomized Controlled Trial 1947 Streptomycin for Pulmonary Tuberculosis

- Population
  - Patients age 15-30
  - Progressive bilateral pulmonary TB
    - Presumably recent (incident cases)
    - Bacteriologically proven
    - Unsuitable for lung collapse therapy
- Intervention
  - Streptomycin plus bedrest
- Control
  - Bedrest alone
- Outcome
  - Mortality at 6 months

Tuberculosis treatment in the 1940s: Broomfield Hospital, near Chelmsford

The First Randomized Controlled Trial 1947 Streptomycin for Pulmonary Tuberculosis

- Trial methods
  - Subjects identified by consultants at time of diagnosis
  - Information sent to coordinating centre
  - If eligible → Admitted to nearest participating hospital
  - Each hospital allocated a series of envelopes bearing only hospital name
    - Each envelope had a card with either S or C
    - One set for men, one set for women
    - Neither the patient or consultant aware of treatment allocation
    - Numerical order based on a series of random numbers
      - Randomization
      - Stratified by gender and hospital
      - Allocation concealment

  - Streptomycin and control patients admitted to different wards, otherwise treated same
  - Prior trials had been controlled but used alternate treatment assignment (?selection bias)
  - End result is the first randomized controlled trial

Random Number Table

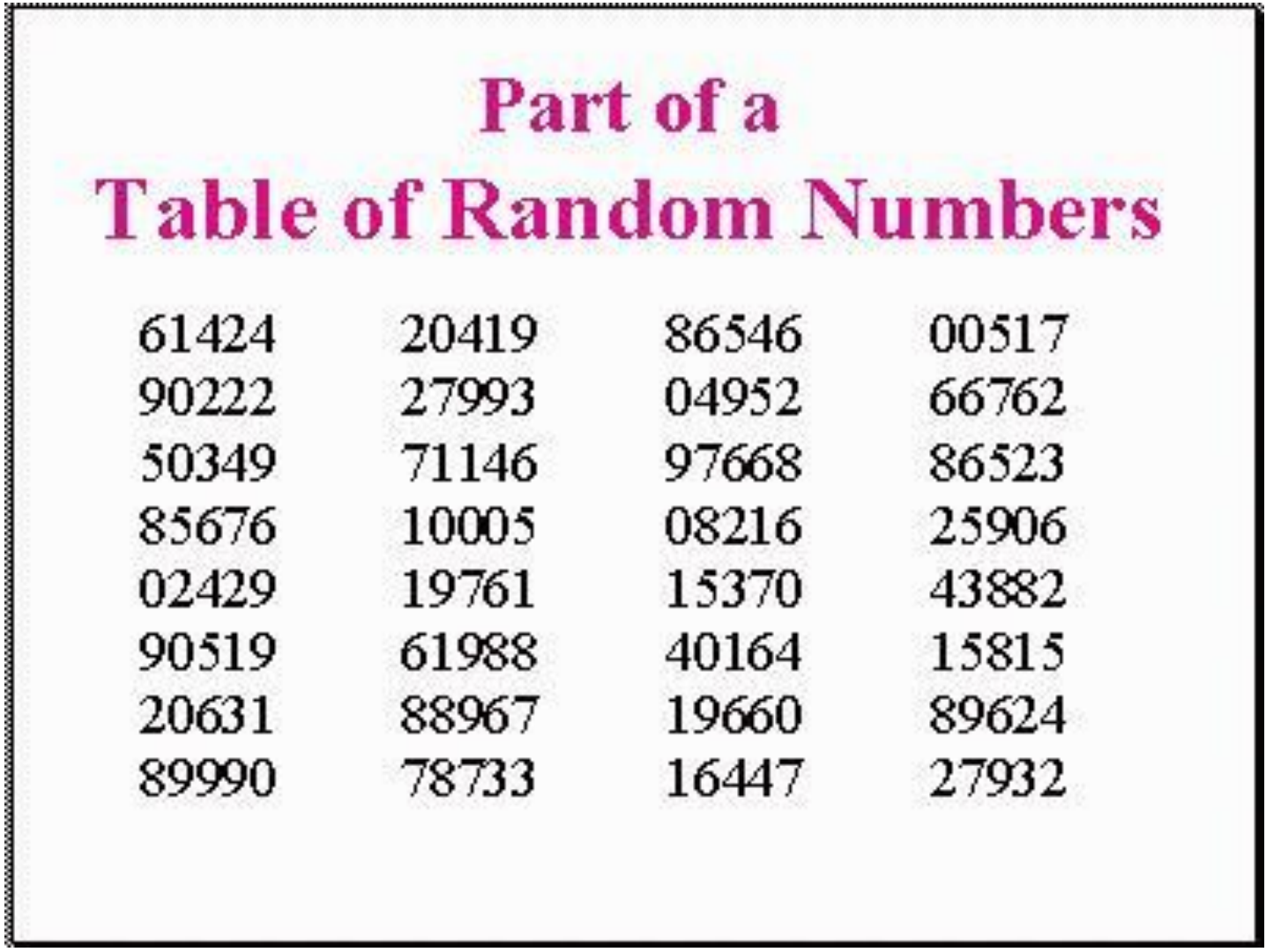
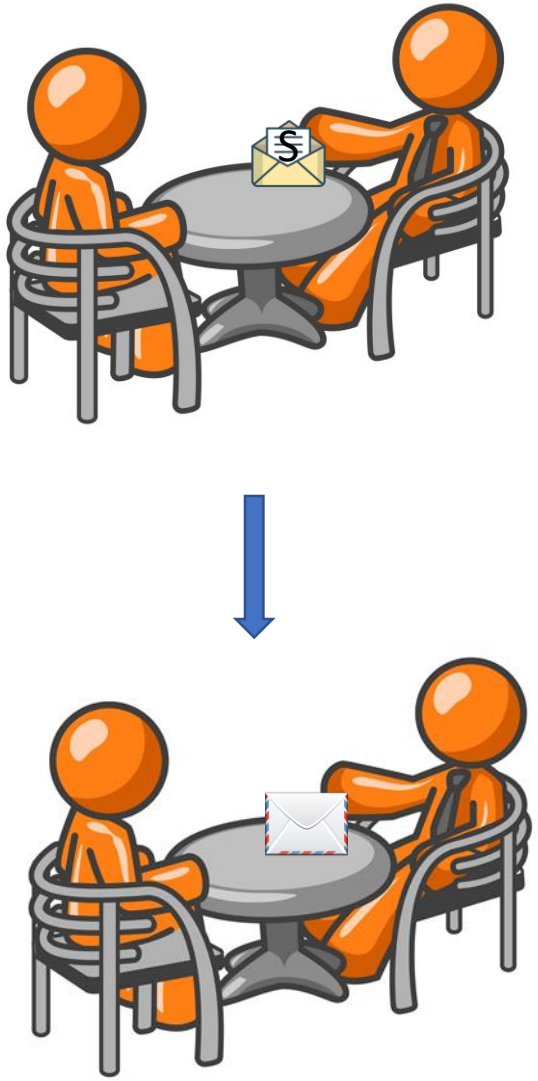


Table B.1: Random Numbers Table

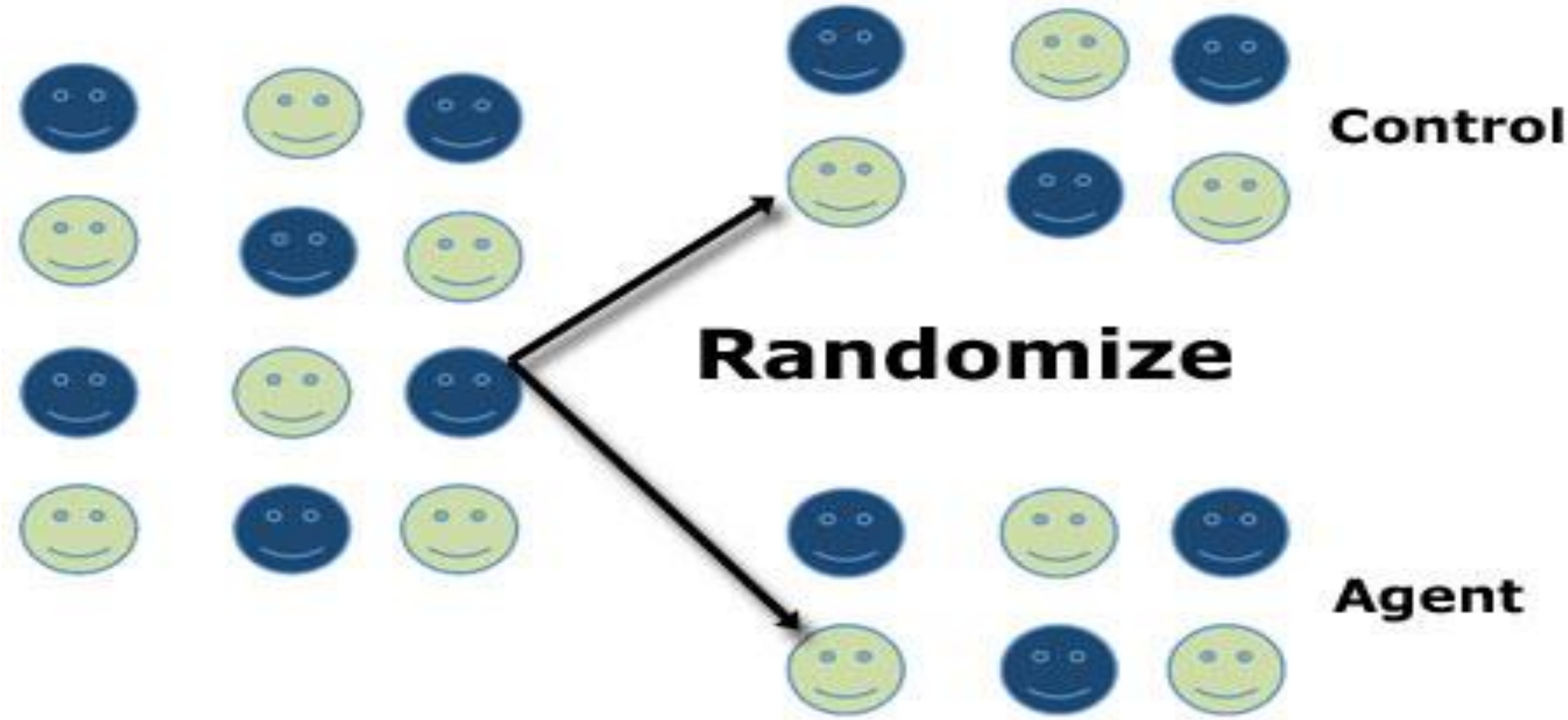
	A	B	C	D	E	F	G	H	I	J
1	8450	6992	6563	0340	2649	6933	9446	6182	2601	7800
2	5952	1443	7100	8444	3904	0159	1849	2601	9763	9058
3	5711	6779	9388	9668	4167	1423	2744	4622	2179	8503
4	2681	8047	0494	7853	8411	5406	8127	9577	8530	2350
5	0739	3114	3997	3482	3226	2216	6874	0620	8521	2938
6	8985	2463	5054	3448	6357	0187	6342	4740	4064	5068
7	7644	9339	8375	4583	7715	6355	6827	2055	9328	3287
8	6277	6631	8797	3693	6370	1436	1599	6267	2758	0323
9	6355	7590	7628	9054	0022	4241	7499	3430	3644	6576
10	7828	0589	3075	1954	5972	2266	0055	1097	9706	9009
11	6026	4546	4119	1554	4895	3123	9849	2094	5062	6711
12	8416	1972	9345	1593	2943	2379	5062	4829	5952	8292
13	1433	8823	7706	5273	6160	2161	5510	8617	7894	0175
14	0622	4884	8113	4447	5735	6347	7280	2301	2330	0693
15	4104	7164	1184	3964	2119	6968	0469	3827	0845	8400
16	4272	4979	1471	0942	9573	4283	1557	0161	3957	2516
17	1225	4171	3433	8700	0042	5884	2508	3250	1520	6366
18	7442	6575	1927	7267	7182	3960	4341	0350	1126	5945
19	4911	9007	3048	0319	0916	3002	1466	4421	7246	7662
20	3143	7402	4486	0909	1858	7961	1211	6296	5545	4588

Benefits of Randomization

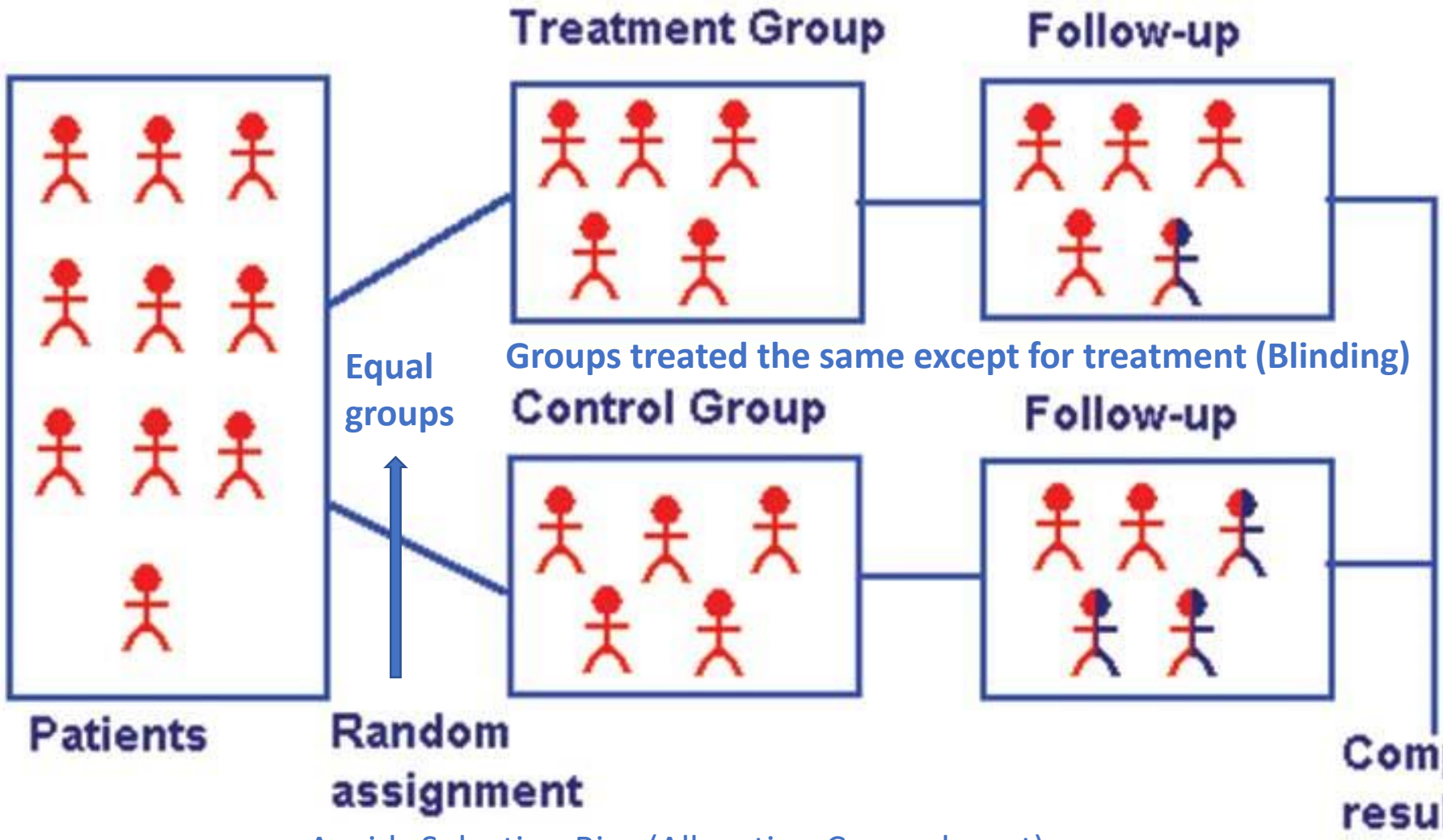
- Controls selection bias
  - Primary benefit (provided there is allocation concealment)
    - Bradford Hill's major concern
    - Alternate assignment subject to bias
- Best means of controlling for the known and unknown confounders in each arm
  - Factors that can affect outcome are randomly distributed
  - Confounders are controlled for even when unknown
- Allows for application of statistical models
  - Assumption that groups are equal at the onset
  - If groups are not equal, results of statistical tests comparing the groups may be invalid



Randomization tends to produce equal groups



Essence of Randomized Controlled Trials (RCTs)



Avoids Selection Bias (Allocation Concealment)

Remdesivir for the treatment of patients in hospital with COVID-19 in Canada:

a randomized controlled trial

Canadian Treatments for COVID-19 (CATCO)*; for the Association of Medical Microbiology and Infectious Disease Canada (AMMI) Clinical Research Network and the Canadian Critical Care Trials Group

*The complete list of authors appears at the end of the article.

n Cite as: CMAJ 2022.doi: 10.1503/cmaj.211698; early-released January 19, 2022

Table 1: Characteristics of patients at baseline in the Canadian Treatments for COVID-19 trial

Characteristic	No. (%)* of patients receiving remdesivir n = 634	No. (%)* of patients receiving standard care n = 647
Age, yr, median (IQR)	65 (53 to 77)	66 (54 to 77)
Female sex	260 (41.0)	255 (39.4)
Clinical Frailty Score median (IQR)	3 (3 to 5)	3 (2 to 5)
Time from symptom onset, to hospital admission, days	6 (3 to 9)	6 (4 to 9)
Time from symptom onset to randomization, days	8 (5 to 11)	8 (6 to 11)
Diabetes†	155 (33.6)	188 (38.4)
Chronic respiratory disease†	67 (14.5)	65 (13.3)
Asthma†	49 (10.6)	55 (11.2)
Smoker†	23 (5.0)	22 (4.5)
Chronic cardiovascular disease	120 (26.0)	135 (27.6)
Chronic liver disease†	8 (1.7)	19 (3.9)

Table 1 MRC Trial		Streptomycin (n=55)	Control (n=52)
Gender (M:F) [% M]]		22:33 [40%]	21:31 [40.4]
General Condition	Good	8	8
	Fair	17	20
	Poor	30	24
Evening Temperature	98-98.9° F	3	4
	99-99.9° F	13	12
	100-100.9° F	15	17
	≥ 101° F	24	19
ESR	0-10	0	0
	11-20	3	2
	21-50	16	20
	≥ 51	36	29

Table 1 demonstrates results of randomization / benefit of stratification

Results of MRC Streptomycin RCT

Table 2	6 Month Mortality				
		Number	Per Cent	Odds Ratio	P value
Streptomycin		4/55	7.2%	0.28	P = 0.03
Control		15/52	28.8%		

Resistance to Streptomycin at 4 months

Adverse Effects: Ototoxicity

The Ethics of Randomization

- Is it ethical to deny subjects with a potentially life-threatening disease access to a promising new therapy?
  - Clinical Equipoise
    - **the equality regarding probability of benefit that must exist between two or more groups being compared in a study.**
    - **provides the ethical basis for medical research that involves assigning patients to different treatment arms of a clinical trial.**
    - "We just don't know if the treatment is "effective" or "safe"
    - Randomization and blinding are helpful

The Ethics of Randomization

- Informed Consent
  - Subjects are aware of the potential risks and benefits of participation, including the randomization process
  - The subjects in the streptomycin trial were not aware they were participating in a research study and did not provide informed consent

- Nuremberg Code 1948

- The Declaration of Helsinki 1964

- The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2)

Nuremberg Code (1948)

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disability injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

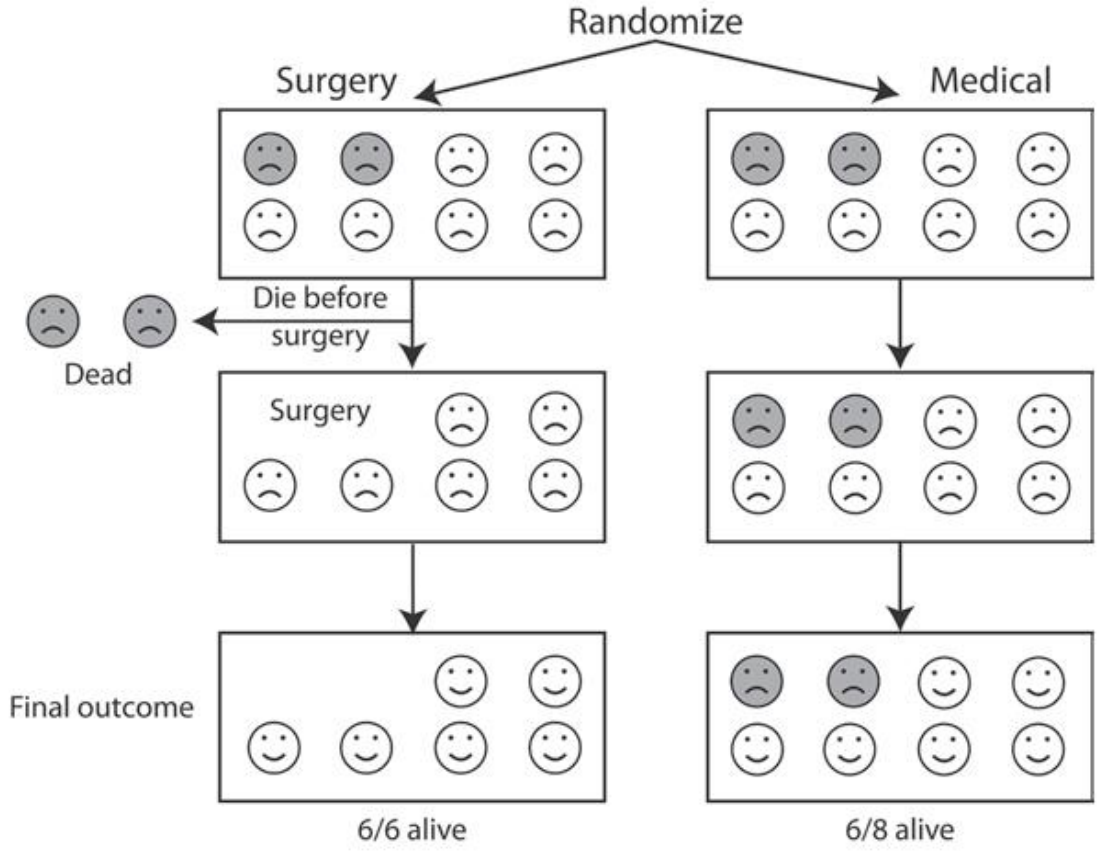
DECLARATION OF HELSINKI :- Basic Principles

1. Conform to accepted scientific principles.
2. Design formulated in experimental protocol, reviewed by IEC.
3. Conducted by qualified and trained persons.
4. Importance in proportion to inherent risk.
5. Assessment of risks vs. benefits.
6. Safeguard subject's integrity (privacy).
7. Abstain unless hazards are predictable.
8. Preserve accuracy when publishing.
9. Adequately inform or right to withdraw.
10. Obtain true informed consent in writing.
11. Reliance on legal guardian.
12. State compliance with Declaration.

TCPS 2

- The Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans **(TCPS** 2)provides ethics guidance that applies to all research involving human participants – including their data and/or biological materials – conducted under the auspices of an institution eligible for funding by the fed (CIHR, NSERC, SSHRC).
    - First edition 1998
    - The official human research ethics policy of the federal research granting agencies in Canada

The Concept of Intention to Treat Analysis



- How do we analyze this data?
- Obviously 75% survival in medical group (6/8)
- What is the survival in the surgical group?
  - 100% (6/6) or 75% (6/8)
  - Should we include subjects who did not receive assigned treatment?
- Intention to treat vs per protocol analysis

Intention to Treat Analysis (ITT)

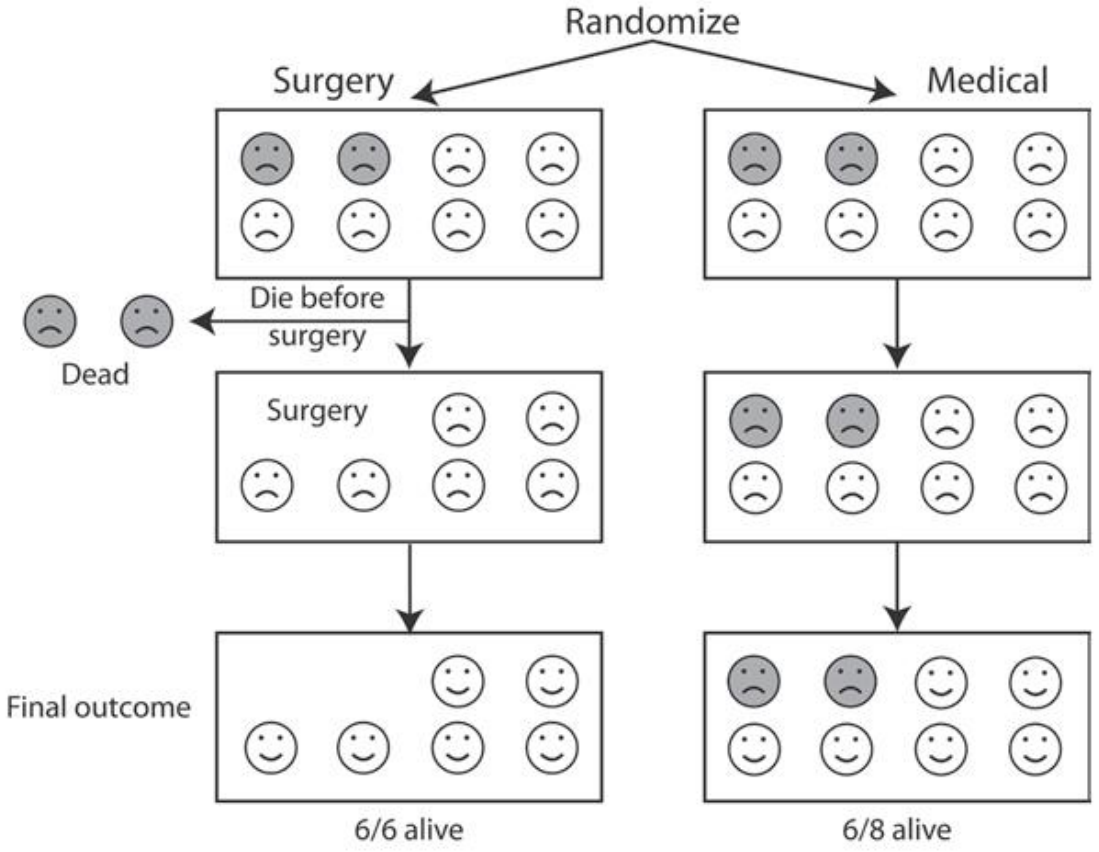
Intention to Treat Analysis

- All subjects are analyzed according to the group to which they were randomized
- Maintains the randomization
  - Guards against bias
  - Theoretical basis for the statistical tests of significance
- ? Measures effectiveness

Per Protocol Analysis (PP)

- Subjects are analyzed according to the treatment which they received
- Some of the benefits of randomization may be lost
  - May introduce bias
  - May invalidate statistical tests
- ? Measures efficacy

Intention to Treat Analysis



- ITT result (survival)
  - 75% surgical vs 75% medical
  - May be a better measure of real world effectiveness of surgery if subjects are dying before they can have surgery (even in RCT)
- PP result (survival)
  - 100% surgical vs 75% medical
  - May need more timely access to surgery
  - Some patients may be too sick for surgery

Intention to Treat should always be the primary analysis

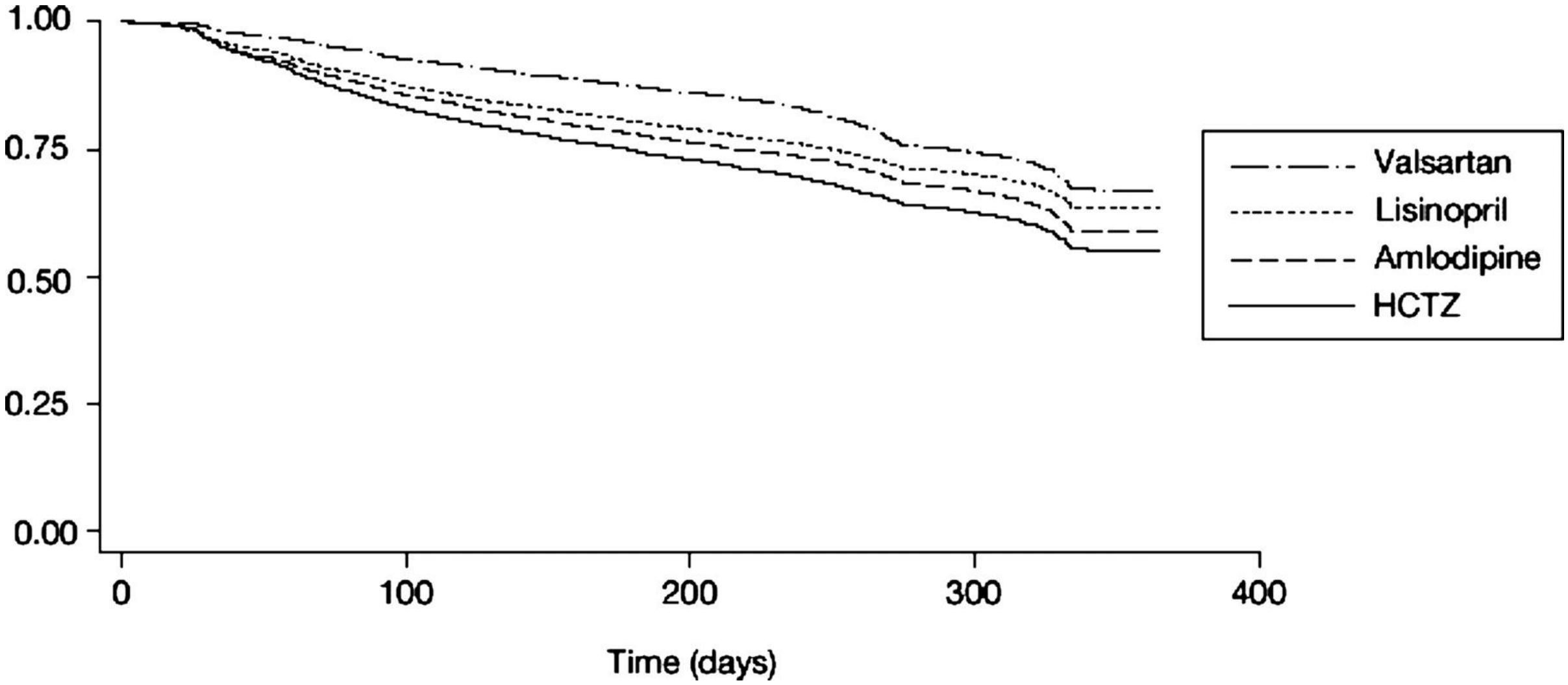
RCTs and Drug Approval by FDA

- To establish a drug's effectiveness, it is essential to distinguish the effect of the drug "from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."
- FDA regulation at CFR 314.126(b) describes characteristics of an adequate and well-controlled clinical investigation, including choice of control, method of patient assignment to treatment (e.g., randomization), adequate measures to minimize bias (e.g., blinding), well-defined and reliable assessment of individuals' response (i.e., efficacy endpoint), and adequate analysis of the clinical investigation's results to assess the effects of the drug (i.e., statistical methods). …….. randomized double-blinded, concurrently controlled superiority trials are usually regarded as the most rigorous design……. And accepted as the "gold standard"

Disadvantages - RCTs

- Limitations of external validity (generalizability)
- Often relatively short treatment interval
  - Long term efficacy not demonstrated
  - True adverse effect profile may not be demonstrated
    - Rare adverse effects
    - Long term adverse effects
  - True rates of drug persistence are not evaluated
    - Achievement of therapeutic goal e.g. blood sugar in Diabetes
    - Symptom control e. g. diarrhea in ulcerative colitis
    - Well tolerated with no adverse effects

Persistance of Antihypertensive Monotherapy



Disadvantages - RCTs

Limitations of external validity

- **Where the RCT was performed**
  (e.g., what works in one country may not work in another)
- **Characteristics of the patients**
  (e.g., include better prognosis / exclude "women, children, the elderly, and common medical conditions"[62])
- **Study procedures**
  (pts may receive Rx/care difficult to achieve in the "real world")
- **Outcome measures**
  (e.g., RCTs may use composite measures infrequently used in clinical practice)
- **Incomplete reporting** of adverse effects of interventions
- **Cost**

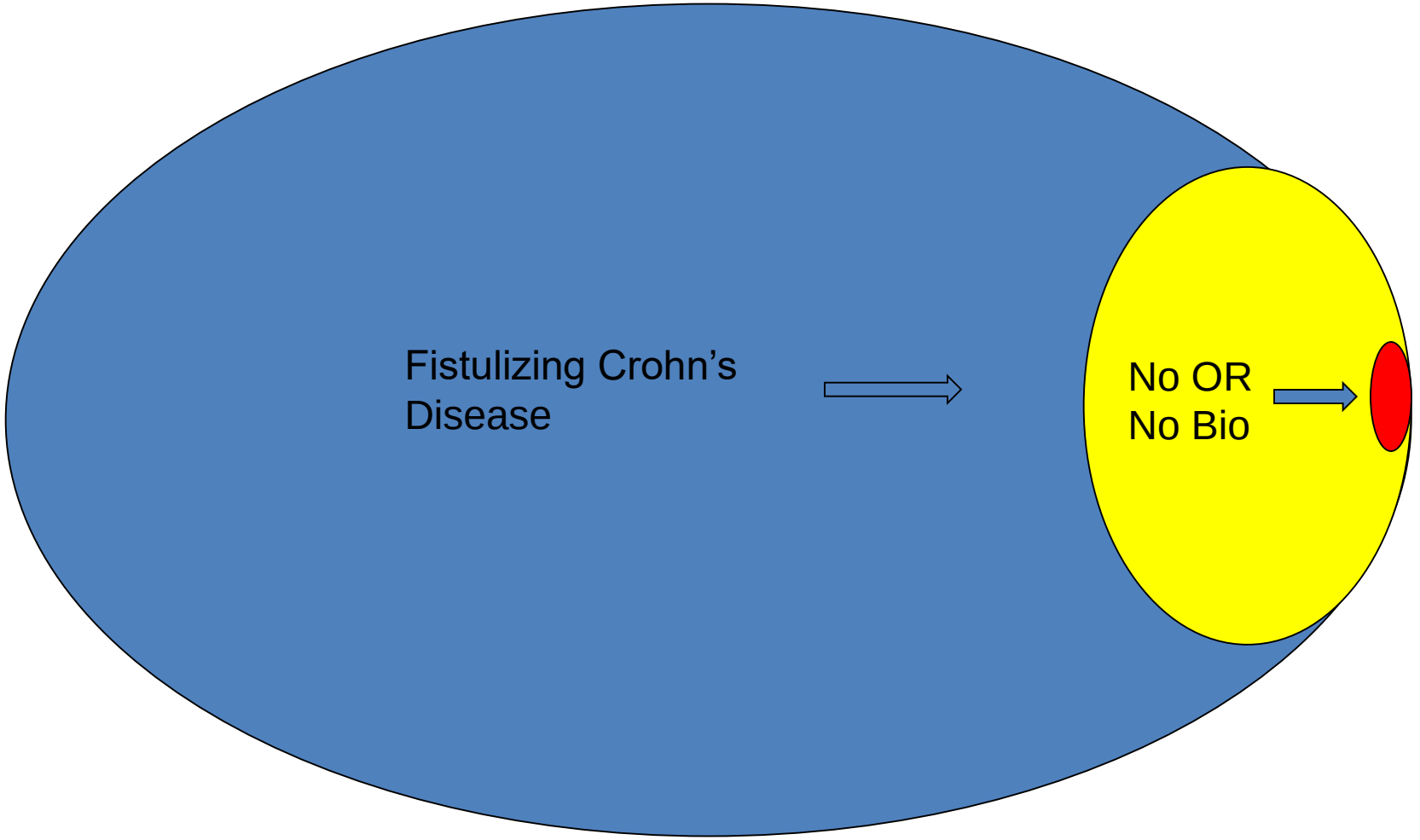
Internal Validity

- Degree to which the results of observations are correct for patients being studied
  - Threatened by
    - Bias within the trial
    - Random variation
- Homogeneous trial population increases internal validity as does randomization, allocation concealment and blinding within the trial

External Validity

- Degree to which the results of observations within the trial may be applied to other patients
  - Threatened by:
    - Strict inclusion criteria
    - Sampling bias
    - Controlled environment of clinical trials
- Generally a balance between internal and external validity is achieved based on the purpose of the study

Diagram of Populations



MD Analytics®

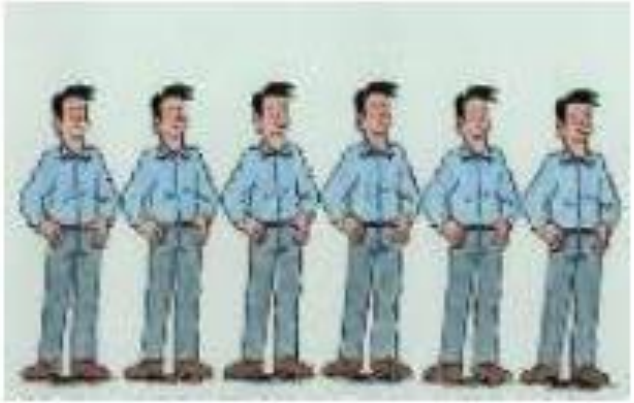
RCT vs. RWE

Randomized Controlled Trial

Real World Evidence

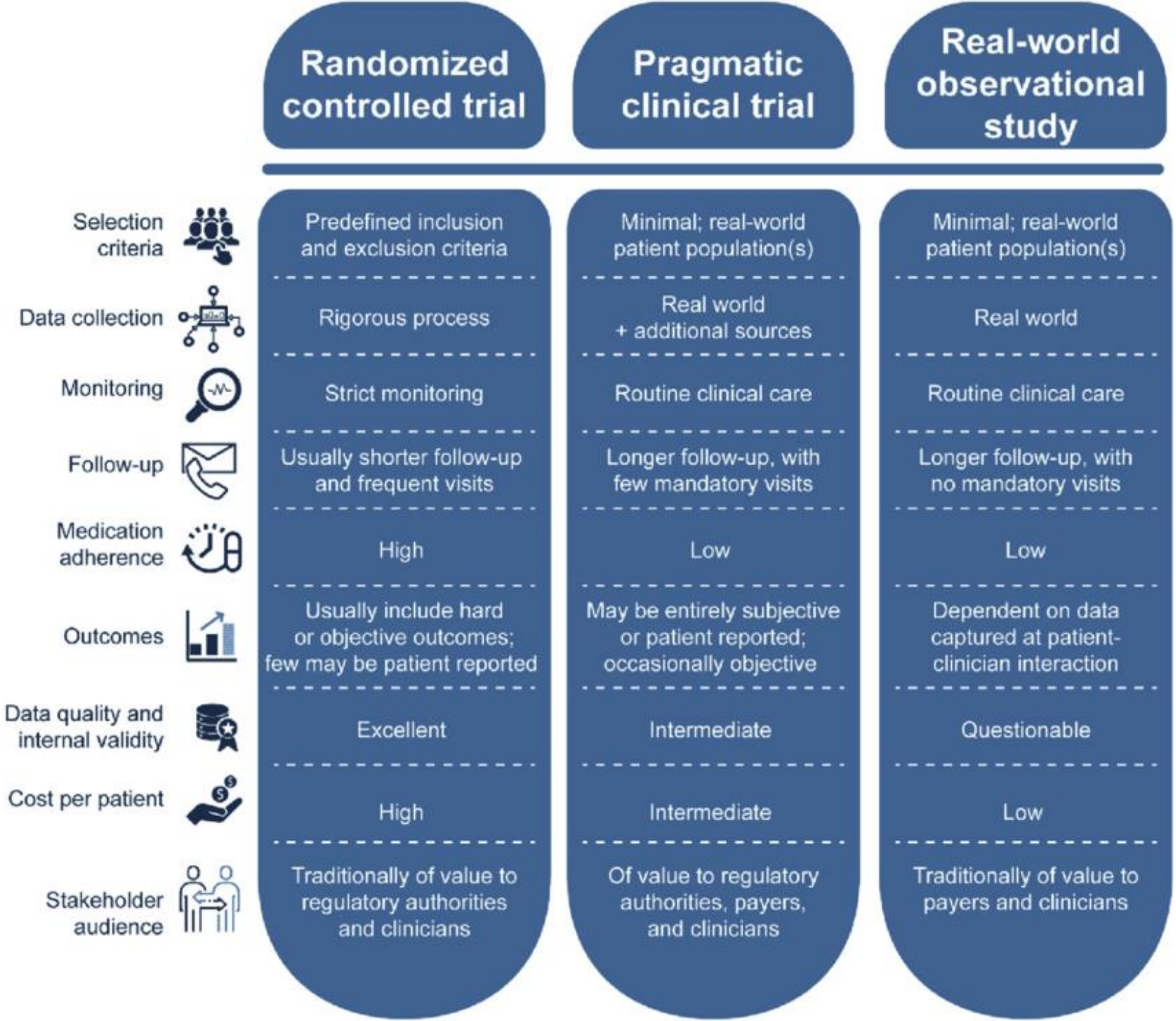
RCT *vs* RWE

- Patient benefit and harm in experimental and closely monitored research studies, normally RCTs.
- Design minimises bias - high internal validity
- Generalisability questionable
  - restricted entry criteria
  - unrepresentative settings



- Patient benefit and harm when the technology is actually applied in everyday practice.
  - pragmatic clinical trials
  - observational studies
  - synthesis
- *ISPOR: "evidence used for decision-making that is not collected in conventional randomized controlled trials (RCTs)"*
- "Dirty" - a lot of variability and biases

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu


Randomized controlled trial
Pragmatic clinical trial
Real-world observational study
Selection criteria
Predefined inclusion and exclusion criteria
Minimal; real-world patient population(s)
Minimal; real-world patient population(s)
Data collection
Rigorous process
Real world + additional sources
Real world
Monitoring
Strict monitoring
Routine clinical care
Routine clinical care
Follow-up
Usually shorter follow-up and frequent visits
Longer follow-up, with few mandatory visits
Longer follow-up, with no mandatory visits
Medication adherence
High
Low
Low
Outcomes
Usually include hard or objective outcomes; few may be patient reported
May be entirely subjective or patient reported; occasionally objective
Dependent on data captured at patient-clinician interaction
Data quality and internal validity
Excellent
Intermediate
Questionable
Cost per patient
High
Intermediate
Low
Stakeholder audience
Traditionally of value to regulatory authorities and clinicians
Of value to regulatory authorities, payers, and clinicians
Traditionally of value to payers and clinicians

RCTs and RWE studies

Refs. SVM Pharma
PWC 2013

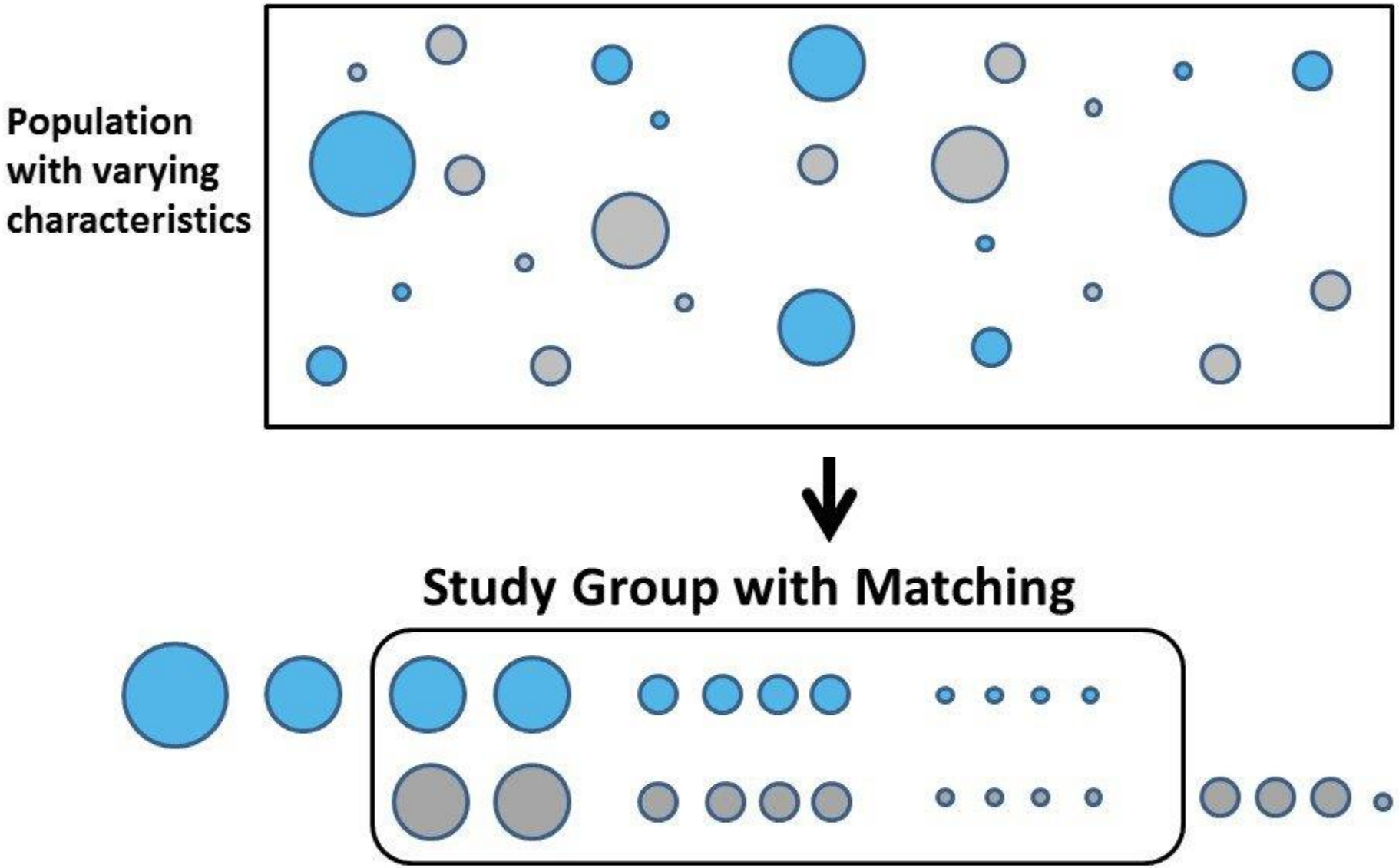
Traditonal RCT model

1. Demonstrates **clinical efficacy** and safety
2. Randomization as an effective tool to **minimize bias and confounding**
3. Limited segment of the population is eligible for inclusion - **questionable external validity & generalizability**
4. **Ideal, controlled setting** ("Good" patient adherence and compliance)
5. Limited ability to investigate costs and value within health systems

RWE model

1. Demonstrates **effectiveness** in the real world of clinical practice
2. **Generalizable** study finding on facts about patient journeys and outcomes
3. Broader & **more representative** of the patient population over a longer time frame
4. **Real world setting** (Busy practices, uncontrolled patients)
5. Demonstrates **value for patients** and benefits within health systems

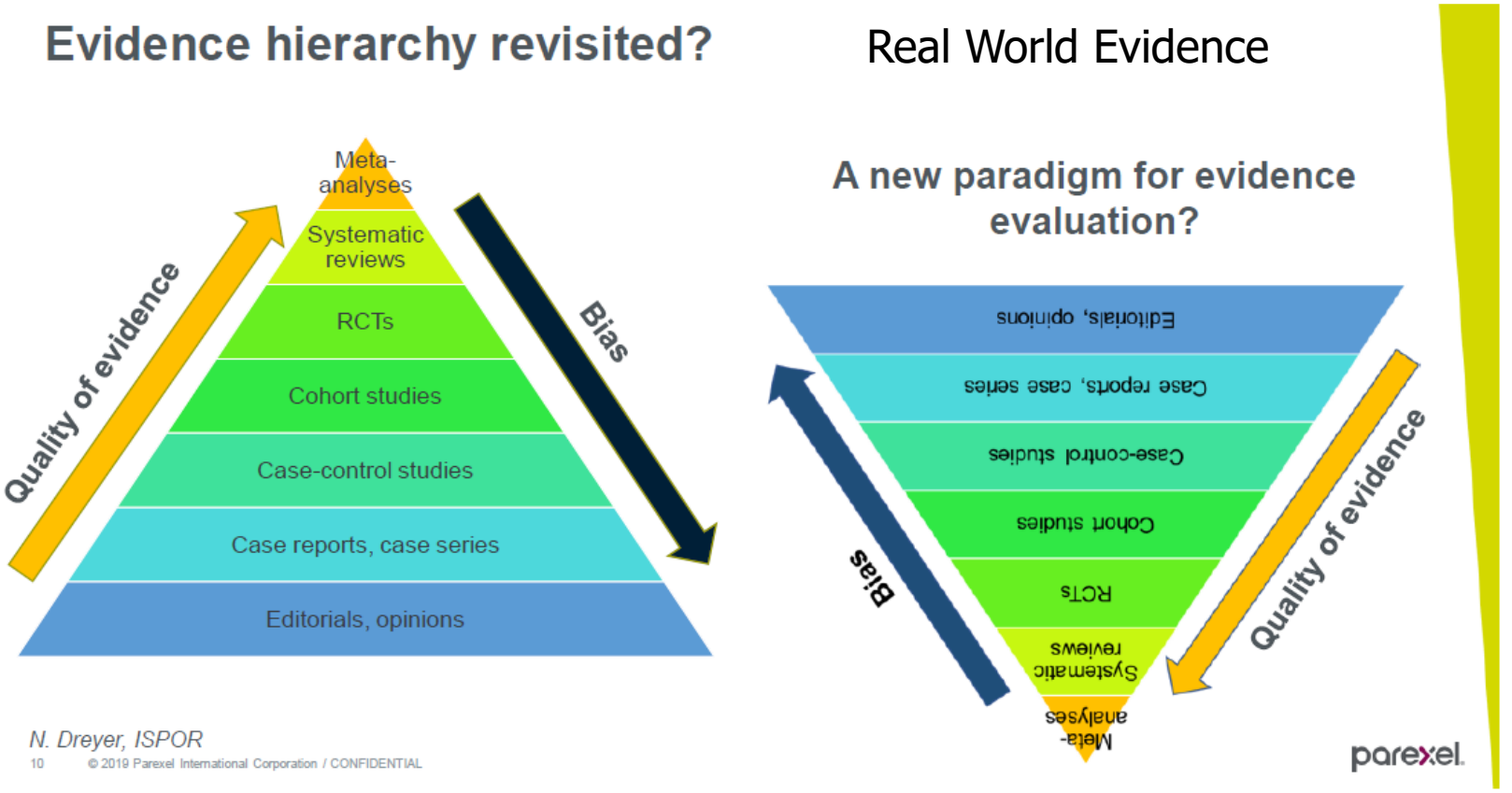
Both groups should be alike with regards to certain variables that might affect the outcome of the experiment


Population with varying characteristics
Study Group with Matching
Treatment
Control

Before/After Propensity Score Matching

Variable	Mean ± SD/%		p-value	Mean ± SD/%		p-value
	FGHM group (n = 265)	HC group (n = 186)		Matched FGHM group (n = 125)	Matched HC group (n = 125)	
Patient characteristics						
Gender (males)	59.2	72	0.005	67.2	67.2	1.000
Age (years)	52.9 ± 10.0	52.1 ± 10.1	0.384	52.0 ± 9.5	51.3 ± 10.3	0.594
BMI (kg/m^2)	25.3 ± 3.6	26.6 ± 10.7	0.087	25.7 ± 3.9	26.9 ± 12.8	0.273
Full-time employment	27.9	54.3	<0.001	47.2	45.6	0.480
Unemployed	35.1	14.0	<0.001	23.2	17.6	0.296
Local public health insurance	17.4	14.0	0.363	12.8	12.8	1.000
Out-of-pocket costs for medical expenses	81.9	84.9	0.444	86.4	86.4	1.000
Drinking	9.1	11.3	0.524	10.4	12.8	0.700
Smoking	23.0	26.9	0.375	23.2	24.8	0.877
Normal INR	93.5	97.8	0.040	98.4	98.4	1.000
Normal hemoglobin	86.8	90.0	0.231	84.0	92.0	0.089
Normal erythrocytes	96.2	98.4	0.255	94.4	98.4	0.182
Cardiovascular comorbidity	11.7	17.7	0.076	11.2	17.6	0.230
Cerebral infarction comorbidity	1.1	3.8	0.100	0.0	5.6	0.265
Previous antiplatelet/coagulants agents	1.9	1.6	1.000	2.4	0.8	0.617

Real World Evidence vs RCT



Propensity Scores

Conclusion

- Randomized controlled trials recognized as “gold standard” for determining efficacy and safety of therapeutic interventions
- Bias mitigated by randomization, allocation concealment, blinding and control within the trial
- Intention to treat analysis preserves the benefits of randomization
- Generalizability of results may be limited due to populations which are enrolled in RCTS
- Real world evidence can provide complementary evidence of treatment effectiveness