BACKGROUND AND OVERVIEW	
Article Title	Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial Yehet al (2018) BMJ; DOI 10.1136/bmj.k5094 PMID: 30545967
Purpose	● To determine if using a parachute prevents death or major traumatic injury when jumping from an aircraft ● Explore issues that can occur with interpretation of clinical trials
Background	● Parachutes are routinely used to prevent death or major injury among individuals jumping from aircraft ● However, evidence supporting the efficacy of parachutes is weak ○ Guideline recommendations for their use are mainly based on biological plausibility & expert opinion ○ No trial data to support their use ● The PARACHUTE (**PA**rticipation in **RA**ndomized trials **C**ompromised by widely **H**eld beliefs abo**U**t lack of **T**reatment **E**quipoise) trial aimed to fill this gap
METHODS	
Study design & methods	● Multisite trial (Sept 2017 to August 2018), 30 day follow up ● Block randomization (1:1) to the intervention (parachute) or control (an empty backpack) ● Intention to treat, not blinded
Selection & enrollment	● Prospective participants were approached by investigators on commercial or private aircraft ○ For the commercial aircraft, passengers seated close to the study investigator would be approached mid-flight ○ Owing to difficulty in enrolling patients at several thousand meters above the ground, recruitment was expanded to include screening members of the investigative team, friends, and family ○ For the private aircraft, the boarding of aircraft was done for the explicit purpose of participating in the trial ● All participants were asked whether they would be willing to be randomized to jump from the aircraft at its current altitude and velocity ● Enrolled individuals willing to participate in the trial & meeting inclusion criteria of study
Outcome measures	● Covariates: demographic data, history of broken bones, acrophobia (fear of heights), previous parachute use, family history of parachute use, and frequent flier status. ● At the time of each jump, researchers recorded the altitude and velocity of the aircraft ● Primary outcome: composite of death and major traumatic injury (ISS >15) within 5 minutes of impact ● Secondary outcomes: Death, ISS at 30 day followup, quality of life at 30 day follow up
RESULTS	
Summary of study results, focusing on outcomes	● 92 were screened, 23 (25%) of whom were enrolled ● Table 2 shows that screened, but not enrolled were ○ Less likely to be on jetliner (0%) vs a biplane or helicopter (100%; p<0.001) ○ At a lower altitude (0.6 m vs 9146 m; p<0.001) ○ Traveling at a slower velocity (0 km/hr vs 800 km/hr; p<0.001) ● No difference in primary or secondary outcomes!!!

Brief summary of main discussion points & study limitations	
Limitations (to state the obvious)	Main issue here is that high-risk populations (i.e. those jumping in the sky) were not enrolled → the "intervention" could not demonstrate large enough effect size ● Red flag to watch out for here is observed rate of primary outcome was very rare ("underpowered") ● Real example [1]: "How long" trial (Lancet hematology, 2017) for DOT in neutropenic fever ○ Compared short course (72h from stable VS) vs standard of care (neutrophil recovery) ○ Safety outcomes similar in short course vs standard of care ○ Not powered for mortality (& trials observed mortality <<< rates in observational data) ● Example [2]: STOP-IT trial (NEJM, 2015) Shorter vs longer course for IAI w/ source control ○ Similar rates of adverse effects in both groups ○ Stopped early due to funding and few immunocompromised patients In the parachute study specifically, the screened population has a systematic discrepancy in exclusion vs randomization (Fig 1, Table 2) ● Because participants & investigators have strongly held beliefs about the effectiveness of "standard of care", they were unlikely to challenge that dogma unless patients were exceptionally low risk (i.e. on the ground) ● Could be applicable for ID as we consider some of our own ingrained beliefs ○ Longer → shorter courses ○ IV → PO ○ Bacteri*cidal* → bacteri*ostatic*
Additional things to consider	As I say in nearly every journal club, "no significant difference" ≠ "not worse than" ● "No significant difference" means "fail to reject the null hypothesis" ■ H0: there is no difference between groups ○ Failing to reject null ≠ null hypothesis has been proved ○ Could mean it was underpowered (as was the case here) ● To "prove" there is no difference, you must disprove one group is worse than the other ■ H0: Empty backpack has a 5% greater mortality than a parachute ○ This would be a non-inferiority trial (likely wouldn't be significant in this case either)
CONCLUSIONS	
Conclusions	● Importance of including details of screened patients (enrolled vs excluded) ○ Not just the breakdown between the arms of the trial ● Although RCTs are considered the "gold standard", their results may not be as clinically relevant as one would think ○ While randomized trials can improve **internal validity** (an accurate assessment of a causal relationship), as equal emphasis should be paid to their **external validity** (the generalizability of results to other populations, settings, situations) ○ My epidemiology mentor would say that "selection bias" is to RCTs as "(residual) confounding" is to observational data ● Not all medical questions should be answered with RCTs. While observational data and mechanistic reasoning can equally have pitfalls, there are cases where they have more clinical significance than RCTs

[1] Aguilar-Guisado M, et al. "Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial". *Lancet Haematology*. 2017. 4(12):e573-e583. PMID: 29153975

[2] Sawyer RG, et al. "Trial of short-course antimicrobial therapy for intraabdominal infection". *The New England Journal of Medicine*. 2015. 372(21):1996-2005. PMID: 25992746