Do single arm trials bring peril to Network Meta-Analyses (NMA)?

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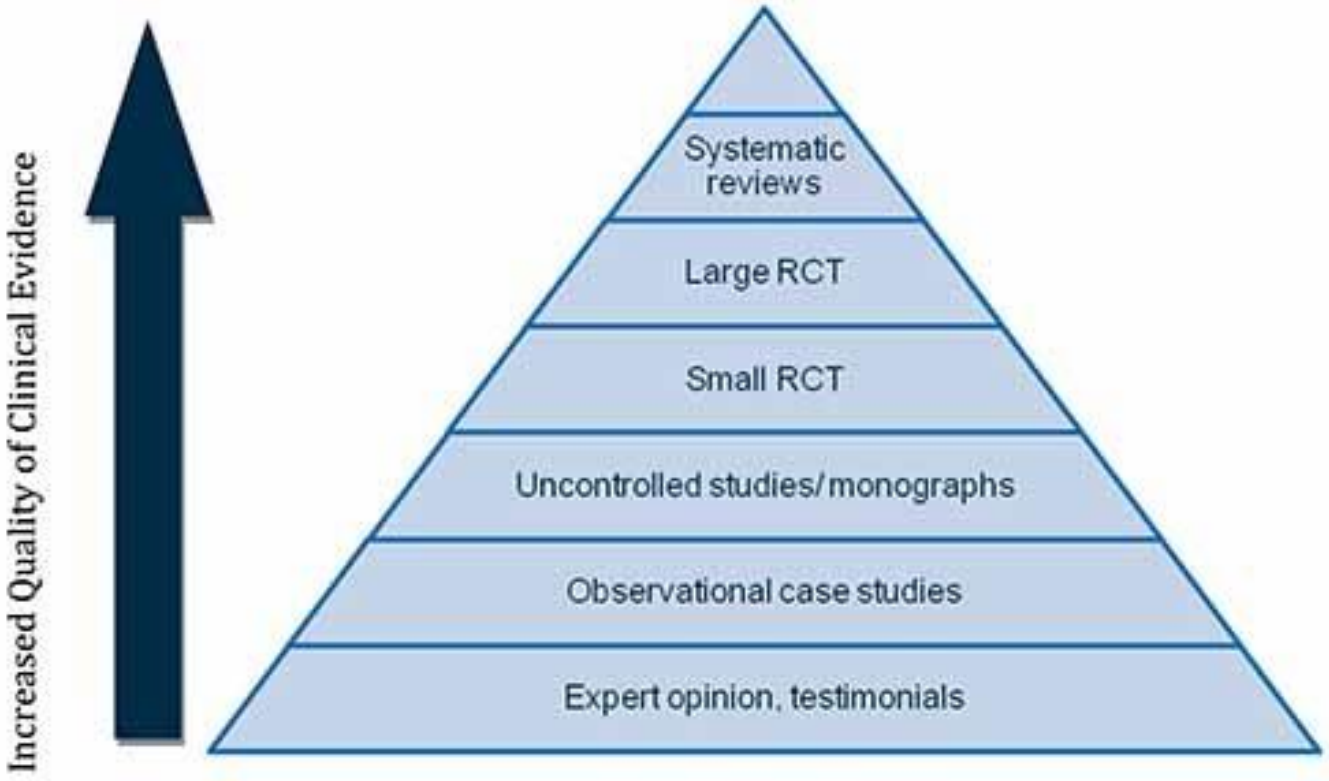
Single arm trials: quality of evidence

Randomized controlled trials (RCTs) allow for causal inference and are therefore the golden standard for comparative efficacy and safety [1,2]

Randomization avoids selection bias by for example, population characteristics (measured / unmeasured)[2]



[1]hhttps://www.nhmrc.gov.au/sites/default/files/images/NHMRC%20Levels%20and%20Grades%20(2009).pdf

[2]Bonnie Sibbald. Understanding controlled trials: Why are randomised controlled trials important? BMJ 1998 Jan 17;316(7126):201:

Justifications for the use of single-arm trials

FDA

Accelerated Approval for Oncology Drug Products[1,2]

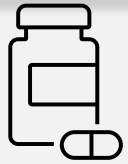
- Serious and life-threatening disease
- Substantial evidence of Efficacy and Safety
- Endpoint reasonably likely to predict clinical benefit
- Meaningful therapeutic benefit over available therapy
- Confirmatory trial

EMA

Conditional Marketing Authorization[3]

- Life threatening and orphan disease
- Benefit-risk balance is positive
- Able to provide data post-authorisation
- Unmet medical need
- Benefit of the medicine's immediate availability is greater than the risk that additional data is required

Other



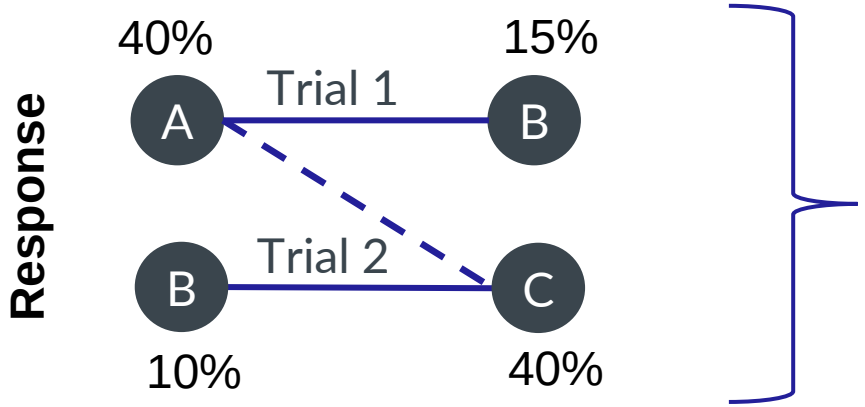
Additional Sources[4-6]

- The mechanism of action is supported by strong scientific rationale and/or preclinical data
- The drug is intended for a well-defined patient population
- Randomization is unethical or infeasible
- Unprecedented effects vs. historic control

1) https://www.fda.gov/media/147925/download; https://www.fda.gov/media/86377/download
2) https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation#criteria-and-conditions-section
3) Simon R, Blumenthal GM, Rothenberg ML, Sommer J, Roberts SA, Armstrong DK, LaVange LM, Pazdur R. The role of nonrandomized trials in the evaluation of oncology drugs. Clin Pharmacol Ther. 2015 May;97(5):502-7
4) Smith GC, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ. 2003 Dec 20;327(7429):1459-61
5) https://www.ema.europa.eu/en/documents/presentation/presentation-role-single-arm-trials-oncology-drug-developmentgideon-blumenthal_en.pdf.

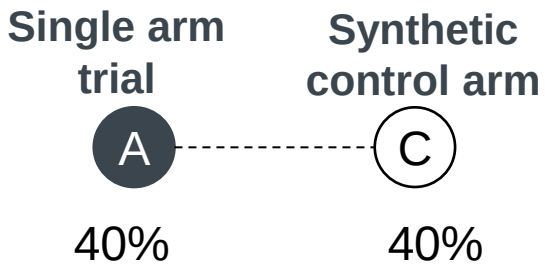
Single arm trials in light of HTA (1)

- FDA/EMA approve drugs based on single-arm trials often with limited patient numbers, follow up and surrogate outcomes[1]
- Payers need to assess whether added benefit is worth added cost based on **unanchored comparisons**
- Comparative effectiveness data sources are prospective/retrospective RWE or historical RCTs



FOR A-C comparison

- Direct unanchored comparison gives OR of 1
- Indirect comparison gives OR of 0.66

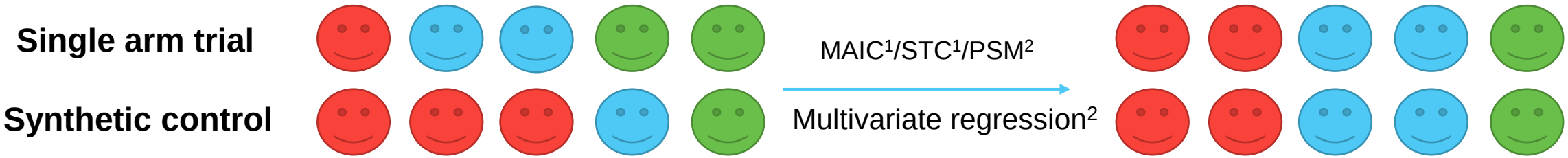


In the example on the left we can see bias of direct comparison by comparing B's, but how do you know bias when considering a single arm trial (example on the right)?

[1]**Ribeiro TB**, **et al**. Comparison of FDA accelerated vs regular pathway approvals for lung cancer treatments between 2006 and 2018. PLoS One. 2020 Jul 24;15(7)

Single arm trials in light of HTA (2)

- There are population adjustment methods to correct for observed differences in (effect modifying / prognostic) baseline characteristics



- Unanchored comparisons assume all effect modifiers / prognostic factors are accounted for, but what about e.g.:
  - Bias due to differences in study design (e.g. immortal time bias, detection bias, selection bias);
  - Bias unobserved heterogeneity (e.g. missing variables in RWE?);
  - Temporal bias;
    - Improvements in subsequent therapies over time (considering overall survival as endpoint in NMA);
    - Quality of care improvements over time;
    - Improved experience by clinicians and thus results over time with therapies?[3]

[1]**Phillippo et al. 2016.** NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE
[2]**Faria et al. 2015.** NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness for Technology Appraisal: Methods for comparative individual patient data.
[3] **Burcu M et al**. Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms. Pharmacoepidemiol Drug Saf. 2020 Oct;29(10):1228-1235.

Use of External Comparators for Health Technology Assessment Submissions Based on Single-Arm Trials

Dony Patel, MSc, PhD, Fiona Grimson, PhD, Elena Mihaylova, MSc, Peter Wagner, Joss Warren, Anke van Engen, MSc, Joseph Kim, PhD

Figure 1. Single arm trial submissions to HTA bodies; Globally, 2011-2019.

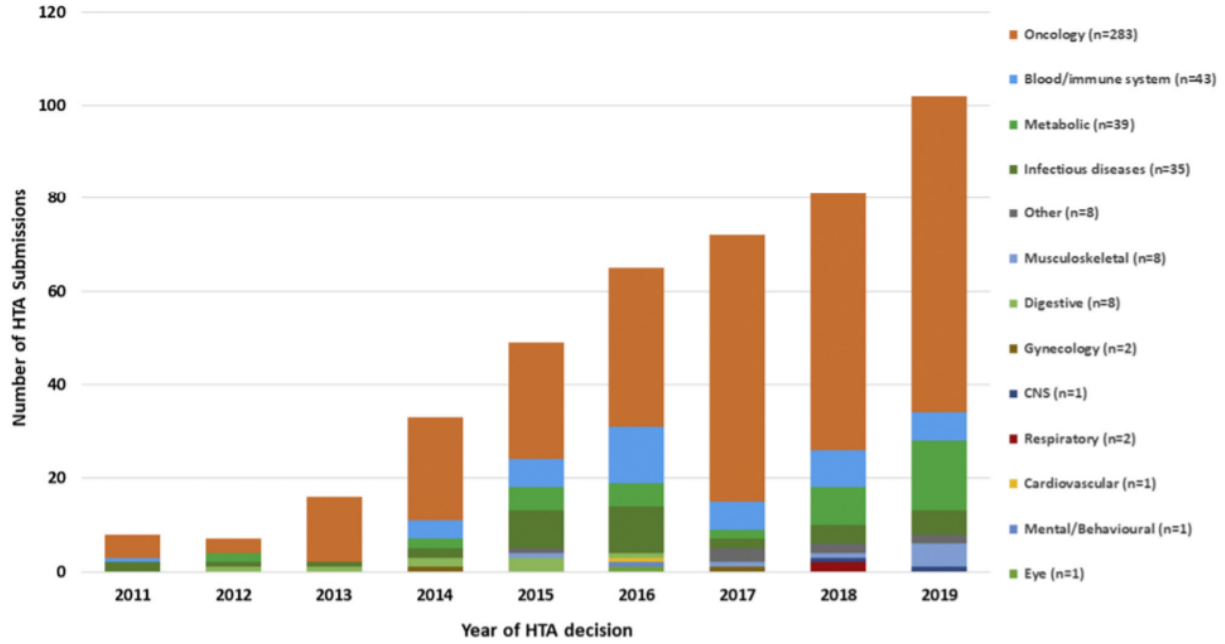


Figure 2. External comparator submissions and outcomes for top 5 HTA bodies by volume, 2011-2019.

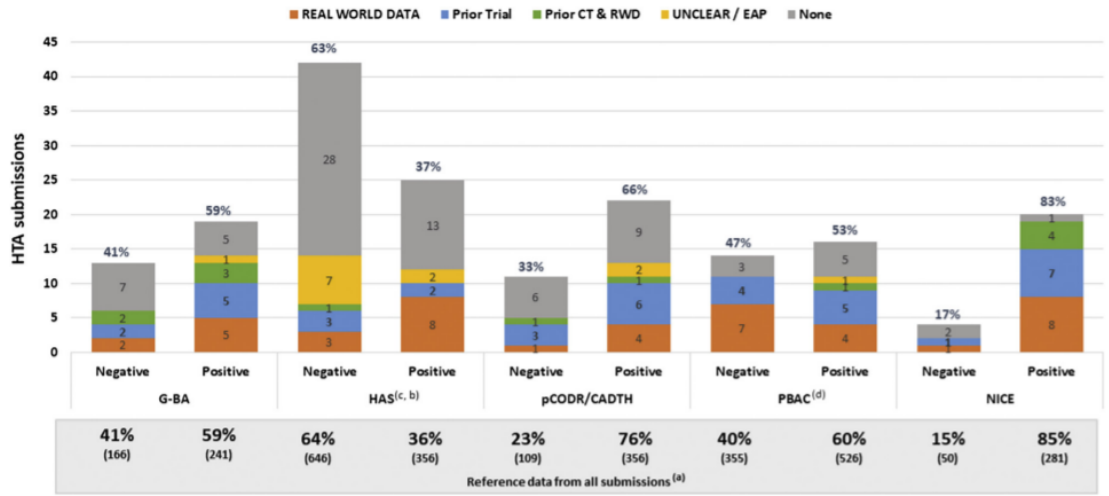


Table 2. Method of comparison by type of external comparator (EC).

Source of comparator data*, n (%)	Method of comparison			Total
	Adjusted ITC	Naïve ITC	Unclear/No EC	
Prior clinical trial	32 (31%)	62 (60%)	10 (10%)	104
Undefined RWD study	8 (22%)	23 (62%)	6 (16%)	37
Prior CT & RWD study	12 (34%)	20 (57%)	3 (9%)	35
Registry	4 (17%)	17 (71%)	3 (13%)	24
Database study	7 (30%)	15 (65%)	1 (4%)	23
Chart review	3 (100%)			3
Grand Total	66 (29%)	137 (61%)	23 (10%)	226

RWD indicates Real World Data; ITC, indirect treatment comparison; CT, clinical trial.
*Categories considered as mutually exclusive for purposes of this analysis.

Key messages

- There is an increase in HTA submissions based on single arm trials
- Type of control data is heterogeneous
- HTA outcomes are heterogeneous
- Comparative effectiveness techniques are heterogenous

Patel D et al. Use of External Comparators for Health Technology Assessment Submissions Based on Single-Arm Trials. Value Health. 2021 Aug;24(8):1118-1125.

Previous recommendations to EMA

How to improve the reliability of Single Arm Trials

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1. A control group should be available for comparison (and considered in study design)
2. The study endpoint should be OS otherwise a bias must be always suspected
3. Historical trends in survival must be accounted for (concurrent controls?)
4. Prospectively planned comparisons with appropriate registry data may be very useful

Comparative effectiveness guidance

- There is regulatory guidance on external controls from FDA[1] and EMA[2]
- There is also the ISPE framework on how to systematically select and consider non-randomised studies (including single-arm trials) alongside RCTs for healthcare decision-making[3]
- There is no current requirement and guidance on how to systematically select external contracts at the point of single-arm trial design

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-10-choice-control-group-clinical-trials-step-5_en.pdf
https://www.fda.gov/media/71349/download
Sarri G *et al.* Framework for the synthesis of non-randomised studies and randomised controlled trials: a guidance on conducting a systematic review and meta-analysis for healthcare decision making. BMJ Evid Based Med. 2020 Dec 9:bmjebm-2020-111493.

Protocol criteria when select external controls

Systematic search to identify

Published trial data	Published RWE data	RWE data-sources

Comparative data quality check[1]

Overlapping prognostic variables	Overlapping outcomes	Quality of recorded prognostic variables and outcomes

Selection of pro- retrospective comparative RWE data[1]

It is crucial that single arm trial inclusion and exclusion criteria are applied, and data is collected transparently and consistently (type of sites, geography, etc.)[2]

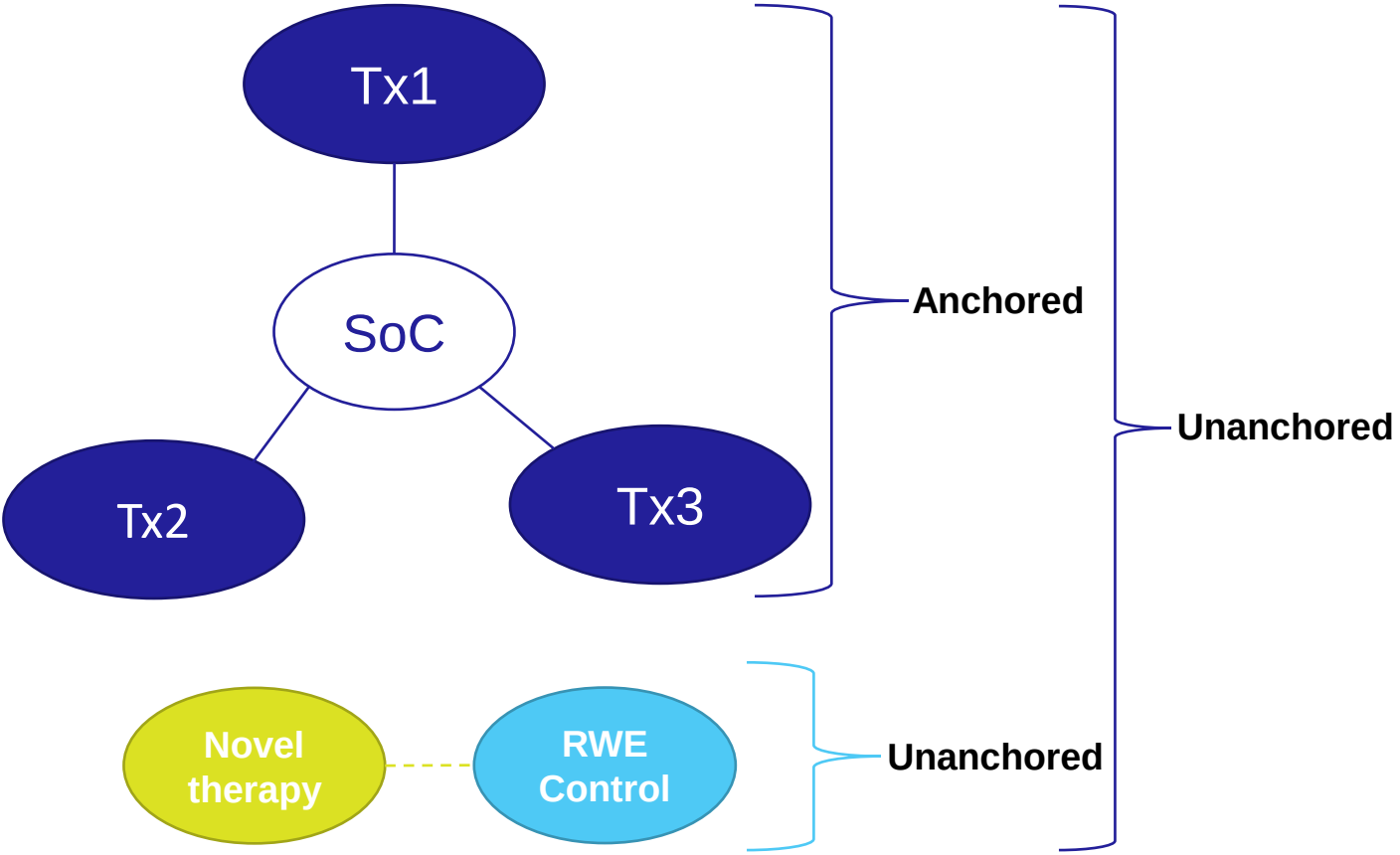
Proposed evidence network or comparator(s)

Statistical methods for handling observed bias

Qualitative description of remaining observed and unobserved bias and proposed methods to quantify this

[1]Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and External Controls in Clinical Trials - A Primer for Researchers. Clin Epidemiol. 2020 May 8;12:457-467.
[2]Burcu M, Dreyer NA, Franklin JM, Blum MD, Critchlow CW, Perfetto EM, Zhou W. Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms. pharmacoepidemiol Drug Saf. 2020; Oct;29(10):1228-1235.

The inclusion of single-arm trials in NMAs



Potential methods to include a single arm trial in ITC

- (Assume) RWE control is SoC and include the unanchored MAIC/STC/naive/PSM comparison in the network as a “two arm RCT”
- Match single-arm trial against one other trial and consider a 3-arm trial in the network
- Assume the placebo arm of the ITC network is representative for the placebo arm of single arm trial

Bayesian hierarchical modelling where single arm based novel therapy is punished with additional random effects

What is the likelihood that EMA/FDA approve a single arm trial for an indication where there are already two or more RCTs that can be considered in a network?

- Novel curative therapies for previously uncurable disease (HEP C)
- Extremely targeted therapies
- Therapies for very rare diseases

Efthimiou et al. 2017. GetReal Work Package 4. Combining randomized and non-randomized evidence in network meta-analysis. Stat Med. Apr 15;36(8):1210-1226.
Leahy J, et al. Incorporating single-arm evidence into a network meta-analysis using aggregate level matching: Assessing the impact. Stat Med. 2019 Jun 30;38(14):2505-2523.
Thom HH, et al. Network meta-analysis combining individual patient and aggregate data from a mixture of study designs with an application to pulmonary arterial hypertension. BMC Med Res Methodol. 2015 Apr 12;15:34.

Single arm trials, are they a peril in NMAs?

Dr. Heeg argues that single-arm trials can be acceptable for HTA purposes under certain conditions, including that the RWE control arm needs to be considered in the single-arm trial protocol."

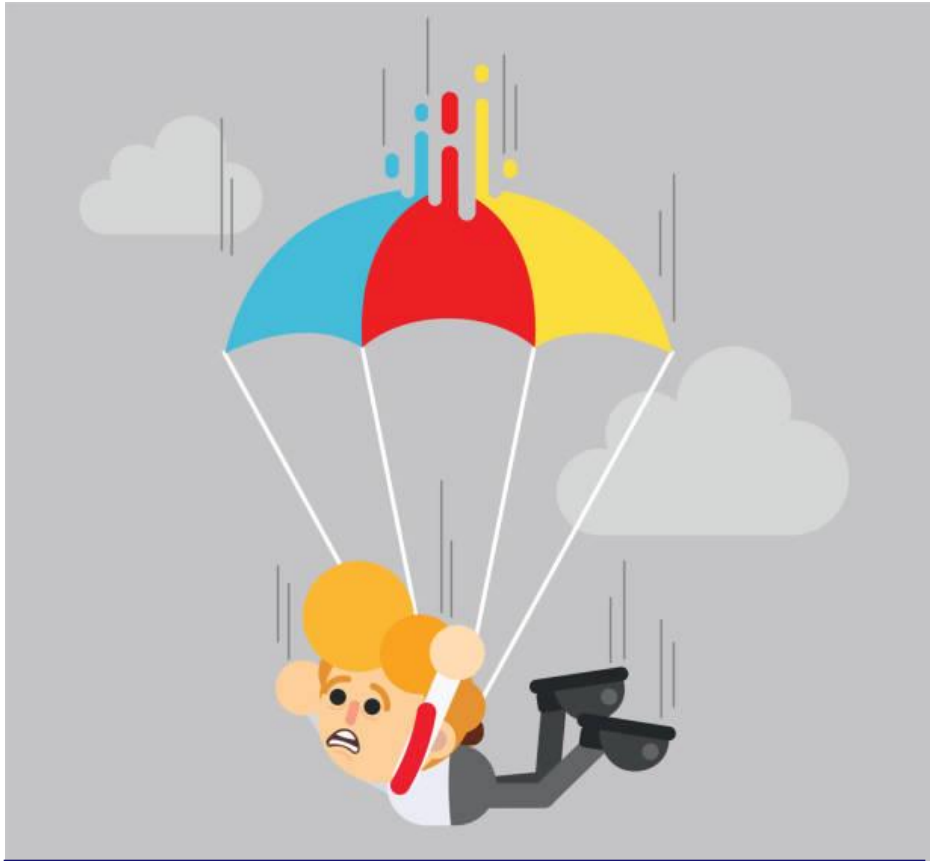
Why?

More and more complex technologies, conditions and evaluations require processing by payer bodies. We therefore need to find ways to incorporate single-arm trials into comparative effectiveness and safety analyses.

By having a transparent and clear framework in how we select, assess and analyse single-arm evidence alongside other study design is needed to reduce this peril.

Recommendations

1. A systematic selection of sources of evidence from published research and considerations into the need for new RWE studies to address gaps and limitations
2. Thorough overview on the overlap of data from other sources of evidence to serve as an appropriate comparator arm
3. Statistical methods for handling observed bias
4. Transparent and qualitative description of remaining uncertainty and bias



See slide 3 (Europe21_Cappelleri.pdf)

Thank you.

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Cytel