Single Arm Studies
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Randomized controlled trials (RCTs) are the gold standard – but are not always feasible or ethical

- Rare/orphan diseases
- Breakthrough therapies
- High unmet medical need

Single-arm trials can be used "when patient populations are extremely small, as in some orphan diseases, and the natural history of the disease is well-characterized and the drug's beneficial effects are large" FDA

44% of EMA oncology approvals in the last decade were based on single-arm trials

> 50% of FDA accelerated approvals have been based on single-arm trials

HTA bodies provide some guidance on use of single-arm trials, but it is limited – except to say that "naïve comparisons

IQWiG

"the Institute can also consider indirect comparisons to assess cost-benefit relations… [however, IQWiG] disapproves of the use of non-adjusted indirect comparisons (i.e. the naive use of single study arms); it accepts solely adjusted indirect comparisons"

NICE

"inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence"

Reimbursement submissions based on single-arm trials have been reviewed

- Access/reimbursement has been possible with only single-arm trials
- Perceived methodological strengths/weakness of any indirect comparisons do not directly correlate with approval/rejection
- Other considerations are efficacy, unmet need, economic model and price

NICE	pCODR	PBAC
Purser et al. 2014	Samjoo et al. 2014	Macaulay et al. 2014
4 submissions between 2009 and 2014	7 submissions between 2011 and 2014 for oncology therapies	5 submissions in 2007 and for oncology therapies
1 received a positive recommendation	4 received a positive recommendation	1 received full approval, 2 restricted approval
The accepted submission used clinical efficacy based on multiple single-arm trials and demonstrated a lack of alternative treatment regimens and significant potential benefits	Accepted submissions demonstrated limited treatment options and infeasibility of RCTs	Approved submissions were based on 'side by side' uncontrolled indirect comparisons to historical controls and/or other trial data

FDA and EMA have approved products based on historically controlled trials

- Of 774 FDA applications between January 1999 and May 2014, 403 were approved, of which 64 indications were based on uncontrolled trials[7]
  - The majority (34) were for hematological malignancies[7]
  - In a review of 49 FDA applications between 2001 and 2015 for high-risk orthopaedic devices, 8 were based on historically controlled trials, and another 2 were based on a combination of active and historical controls[6]
- During the same period, out of 795 applications, EMA approved 415, of which 44 indications were based on uncontrolled trials[7]
  - Another review reviewed EMA applications between January 1995 and December 2015, determining that 51 out of 723 approved drugs were approved based on non-RCT evidence[13]
    - 58% were for cancers, particularly leukemias and lymphomas

Why pharma-companies do single arm trial?

- Rare or ultra rare condition
  - Small sample size
- Dramatic clinical benefits
  - Large magnitude of difference versus SOC
- Ethical issues
  - Not withholding a beneficial treatment
- Feasibility issues
  - Faster recruitment
- Availability of robust data for historical comparison
  - Use of RWD for comparison

Benefit risk analysis

- Benefit
  - Early filling for approval
  - Acceptability by Regulator validated
  - Lower cost
    - Effect size
    - Logistic
- Risk
  - Acceptability by HTA
  - Difficulty to adjust on confounding variables
  - Predictability of the results

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