From a regulatory perspective: What can we gain from TTE?

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All examples rely on data from publicly available sources (EPAR, SmPC). They are presented for illustration purposes and should not be misunderstood as criticism of the product or associated regulatory decisions.

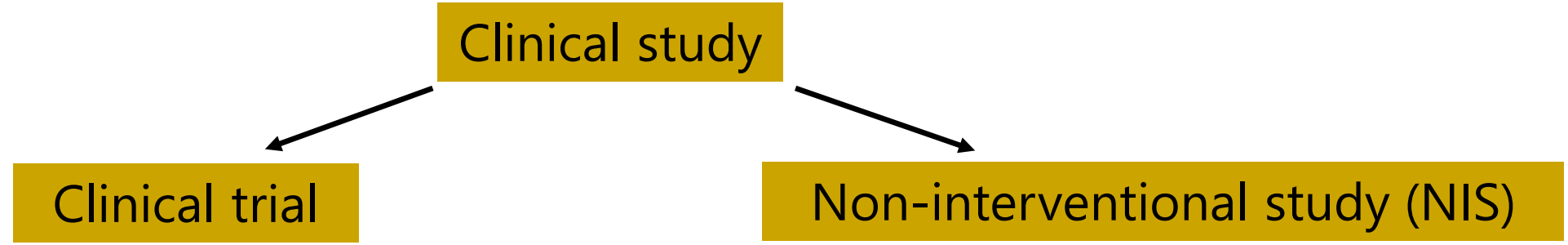
What can we expect from TTE?

A plea for caution

- Questions around comparative safety, efficacy or effectiveness should ideally be addressed with an RCT.
- Evidence from RCTs is considered stronger.
- TTE should not be used as justification to do fewer RCTs.
- If non-RCTs are presented, TTE can
  - reduce the risk of bias and
  - increase transparency.
- Use of TTE should not be limited to non-interventional studies.

Potential applications in regulatory interactions

Where TTE might be useful



- Cohort studies
- Pragmatic trials
- External controls
- Hybrid controls
- …

- Cohort studies
- Case-control studies
- Test-negative design
- …

CP on external controls
out for public consultation.

Some guidance on use of TTE
in RP on use of RWD in NIS.

Deviations from clean RCT

Is TTE useful for every clinical study deviating from a clean RCT?

Some examples:

- In a nationwide pragmatic RCT subjects made a vaccination appointment and were afterwards randomized to vaccination or no vaccination. Rescheduling was only relevant for subjects allocated to the active arm.
- During Covid-19 pandemic some vaccination trials suggested to send the control group to public vaccination centres.

Specifying the target trial might be useful

- for defining the targeted treatment effect,
- for discussing limitations of the implemented trial,
- for identifying measures to reduce the bias.

Case-control studies of regulatory relevance

Where do we encounter case-control studies?

- Usually after marketing authorization, eg. variation or post-marketing measure
- Different levels of data availability ranging from
  - Nationwide numbers of cases, exposures but no characteristics

  to
  - follow-up of cases and controls by direct contact.
- Often encountered with vaccines to estimate vaccine effectiveness after authorization based on immunogenicity (putative correlate of protection):

  Covid-19, FSME, Pneumococcal disease…
- Possible variations of the case-control design:

  Indirect cohort design (Broome method), test negative design, screening method…

Ixchiq

Example of a test-negative (TN) study

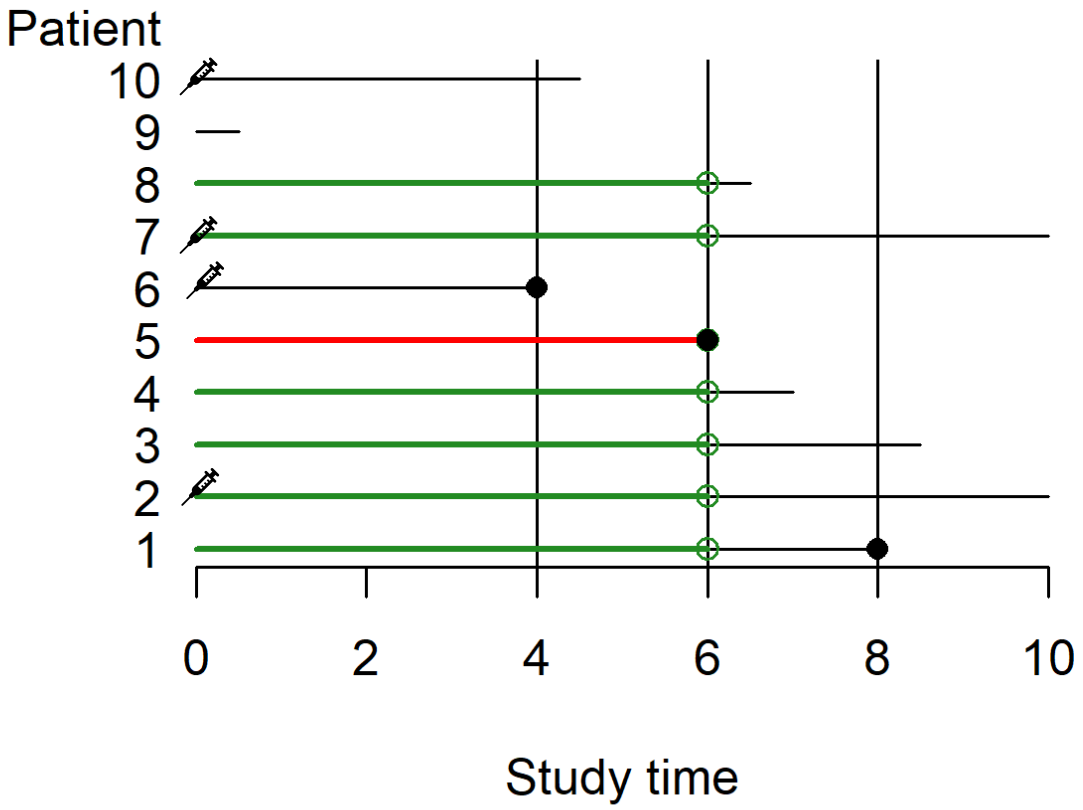
- First approved vaccine for prevention of chikungunya
- Authorization based on immunogenicity data
- Post-approval test-negative effectiveness study planned:
  - Eligbility: 12 yrs, performed RT-PCR testing to investigate CHIKV infection
  - Target sample size of 446 cases (positive test) and 892 controls (negative test)
  - Exposure: vaccination >= 14 days before onset of symptoms
  - Potential confounders: health centre, calendar time of onset, age, sex, number of chronic conditions
  - routine data bases, potentially augmented by interviews
  - Conditional logistic regression to estimate crude and adjusted odds ratios

- Can TTE help us to better understand the estimates from a test-negative design?

TTE for case-control studies

Detour via cohort studies

Case-control study ⟷ Cohort study ⟷ Target trial



With incidence density sampling the matched odds ratio of cases and controls is equivalent to rate ratio in full cohort (Greenland et al,1982).

Implies that case-control studies should use similar temporal structure as cohort studies (time zero, time-varying treatments, baseline covariates…).

(Dickerman et al, 2020)

Test-negative design

One step further

- Naturally reduces bias from health-care seeking behavior.
- Conditioning on receiving a test is a form of post-baseline stratification which may result in selection bias.

Example: Li et al, 2024 estimated effectiveness of BNT162b2 against Covid-19 based on data from the U.S. Department of Veterans Affairs

- Four different design types:
  - Cohort study emulating a target trial (matched vaccinated and unvaccinated individuals, censoring of matched pairs if control got vaccinated)
  - Case-control sampling of the cohort (incidence density sampling)
  - Case-control sampling restricted to person-days with a test
  - Test-negative design

Comparison of designs

Does it make a difference?

Vaccine effectiveness of BNT162b2 for documented SARS-CoV-2 infection (Li et al, 2024)

	Cases	VE, % (95% CI) with rich data set [a]	VE, % (95% CI) with limited data set [b]
Target trial emulation - Cohort	2808	63.6 (59.5, 65.9)	52.3 (48.7, 54.3)
Target trial emulation - Case-control sampling	2808	63.5 (59.3, 65.7)	
Case-control sampling restricted to test days	2798	59.6 (54.2, 62.9)	
Test-negative design	14159	66.3 (63.9, 68.5)	69.3 (67.8, 70.8)

[a] adjusted for calendar date, age, sex, race, urban residence, geographic location, smoking status, body-mass index, number of SARS-CoV-2 PCR tests previously received, and number of influenza vaccinations over the previous five years

[b] adjusted for calendar date, age, sex, race and geographic location

Conclusions

- TND does not explicitly emulate a target trial.
- However, specifying the target trial might help to identify risk for bias.
- Temporal structure should be clearly defined for TND.
- Cohort studies based on TTE usually require adjustment for richer set of confounding variables.
- Negative control outcomes can help to identify bias by unmeasured confounders.
- Not always clear whether to prefer TND or cohort studies based on TTE.

- TTE is not only useful for non-interventional studies but might be useful for any trial deviating from clean RCT.

References

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