Refining the Estimand Framework for 'Trials within Cohort' (TwiCs) Studies

Providing Tailored Guidance

Dr. R. Gal, Clinical epidemiologist
On behalf of L.A. Daamen, R. Kessels, S.A.M. Gernaat, D.R. Mink van der Molen, K. Luijken, G.C.M. van Baal, R.P.A. van Eijk, A.M. May, J.B. Reitsma, E. Schuit, P.M. van de Ven, H.M. Verkooijen

Division of Imaging and Oncology & Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht, the Netherlands

Staged-and-Tailored Informed Consent Symposium
13th September 2023, Online

UMC Utrecht

No conflicts of interest to disclose.

Lessons learned

BRIEF REPORT

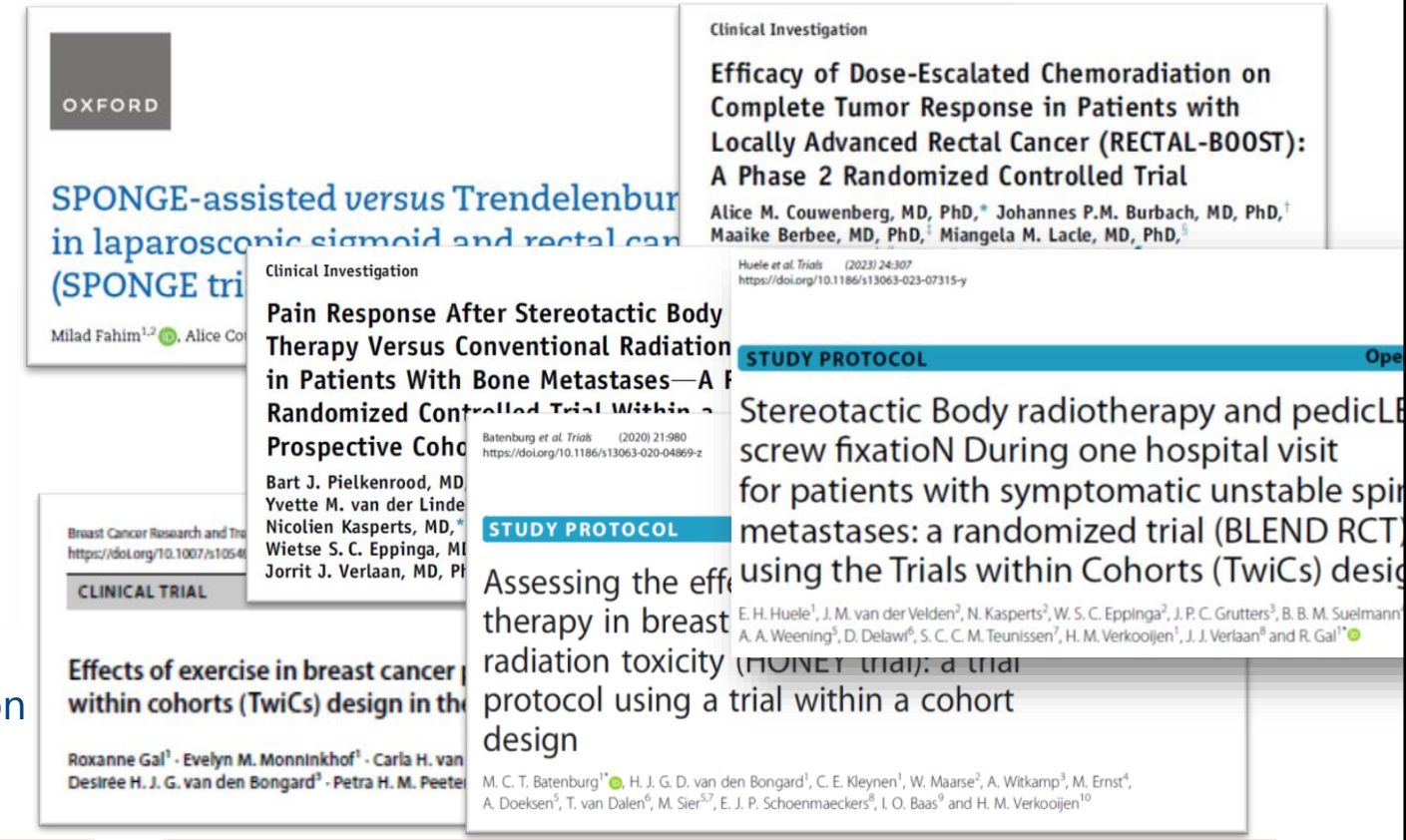
Epidemiology • Volume 27, Number 3, May 2016

Staged-informed Consent in the Cohort Multiple Randomized Controlled Trial Design

Danny A. Young-Afat,[a,b] Helena A. M. Verkooijen,[c] Carla H. van Gils,[a] Joanne M. van der Velden,[b] Johannes P. Burbach,[b] Sjoerd G. Elias,[a] Jonannes J. van Delden,[d] Clare Relton,[e] Marco van Vulpen,[b] and Rieke van der Graaf[d]

1st stage at cohort enrollment: future randomization
2nd stage post-randomization: experimental intervention

Ongoing and completed oncological trials



Intervention offered post-randomization

- Refusal rates ⇧
- Only in intervention group
- Selective?

Reliance on cohort data for endpoint data collection

- Missingness of data ⇧
- Especially in control group
- Selective?

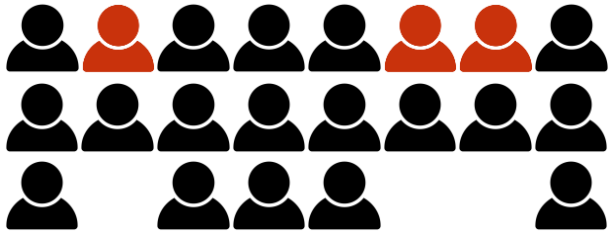
Estimand framework

Treatment effect? ⇨ Randomized controlled trial (RCT)

For example Trial on medication ⇨ some patients need rescue medication

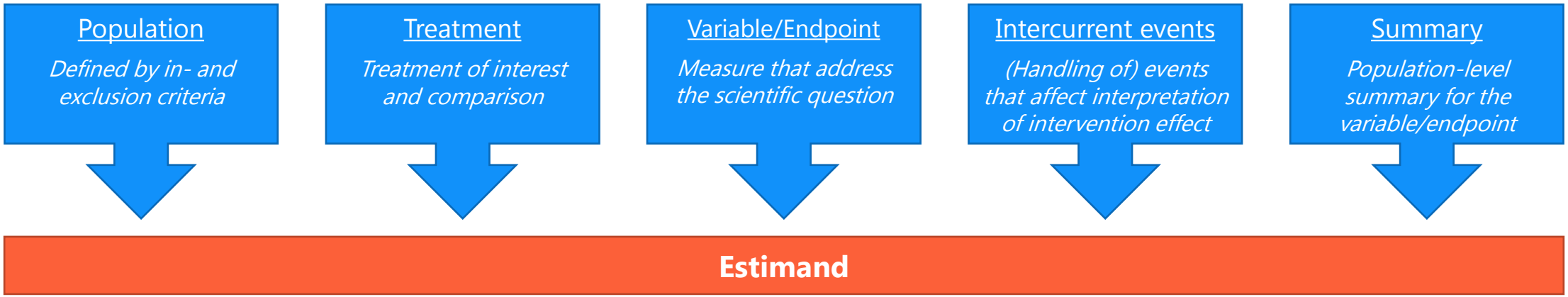
What is the treatment effect …

- … regardless of receiving rescue medication?
- … in the hypothetical condition that rescue medication was not available?
- … in the stratum of population that does not require rescue medication?



Reliable estimations? Acceptable for decision making?

Estimand framework



Estimand:

A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

UMC Utrecht

Strategies for handling of intercurrent events

Treatment policy	Occurrence of IE irrelevant, follows ITT analysis
Hypothetical	Hypothetical scenario in which IE would not have occured
Composite	IE is informative for intervention effect and therefore incorporated in endpoint
While on treatment	Response prior to IE is of interest
Principal stratum	Restricting to a subpopulation in which IE would not occur

Sponge trial

Effect of sponge-assisted surgery instead of use of Trendelenburg position (usual care) on the duration of hospital stay in sigmoid or rectal cancer patients undergoing lacroscopic colorectal surgery?

Population

Defined by in- and exclusion criteria

Patients with sigmoid or rectal cancer, planned for elective colorectal laparoscopic/ robotic surgery

Treatment

Treatment of interest and comparison

Intervention: Sponge-assisted surgery

Control: Trendelenburg position during surgery (usual care)

Variable/Endpoint

Measure that address the scientific question

Duration of post-operative hospital stay

Summary

Populations level summary for the variable/endpoint

Difference in median duration of post-operative hospital stay

Intercurrent events

Events that affect interpretation of intervention effect

IE1 *Intervention arm*: no 2nd stage consent after randomization to intervention

IE2 *Intervention arm*: usual care, despite 2nd stage consent for intervention

IE3 *Control arm*: intervention, despite randomization to control

UMC Utrecht

Sponge trial

Intercurrent events
Events that affect interpretation of intervention effect

IE1	*Intervention arm*	no 2nd stage consent after randomization to intervention
IE2	*Intervention arm*	usual care, despite 2nd stage consent for intervention
IE3	*Control arm*	intervention, despite randomization to control

Population *Defined by in- and exclusion criteria*	**Treatment** *Treatment of interest and comparison*	**Estimand** *Research question*	**Strategy for handling IE's** *Handling of intercurrent events*
ITT population	**Intervention**: Sponge-assisted surgery, **allowing switch to control** **Control**: Usual care, **allowing switch to intervention**	**Effect of offering** sponge-assisted surgery **as primary intervention** instead of usual care **as primary intervention**?	**IE1-3 Treatment policy** (*occurrence of IE irrelevant, follows ITT analysis*)
Intervention accepters	**Intervention**: Sponge-assisted surgery, **allowing switch to control** **Control**: Usual care, **allowing switch to intervention**	Effect of sponge-assisted surgery **as primary intervention** instead of usual care **as primary intervention** **in the subpopulation of patients who accept sponge-assisted surgery when offered**?	**IE1 Principal stratum** (*restricting to a subpopulation in which IE would not occur*) **IE2-3 Treatment policy**
Intervention and control compliers	**Intervention**: Sponge-assisted surgery, **not allowing switch to control** **Control**: Usual care, **not allowing switch to intervention**	Effect of sponge-assisted surgery instead of usual care **in the subpopulation of patients who accept and undergo each of these two treatments when offered**?	**IE1-3 Principal stratum**
Intervention accepters	**Intervention**: Sponge-assisted surgery, **allowing switch to control** **Control**: Usual care, **not allowing switch to intervention**	Effect of sponge-assisted surgery **as primary intervention** instead of usual care **without allowing switch to sponge-assisted surgery** **in the subpopulation of patients who accept sponge-assisted surgery as primary intervention when offered**?	**IE1 Principal stratum** **IE2 Treatment policy** **IE3 Hypothetical** *(hypothetical scenario in which IE would not have occurred)*

Conclusion

The estimand framework …

- … guides definition of the treatment effect to be estimated that reflects the (clinical) research question,
- … thereby addressing intercurrent events specific for TwiCs,
- … facilitates aligning the research question, trial design and statistical analysis when planning a trial.

"Answering the wrong questions is bad science.
Therefore, basing regulatory decisions on answers to the wrong questions is bad policy."

Work in progress:
Refining the Estimand Framework for 'Trial within Cohort' (TwiCs) Studies: Providing Tailored Guidance

UMC Utrecht