Improving efficiency in both interim and final analyses

UNIVERSITEIT GENT

Kelly Van Lancker
joint work with Stijn Vansteelandt and An Vandebosch

Janssen

Plan

1. Improving Efficiency of Final Analysis

2. Improving efficiency of Interim Analysis

Potential of baseline covariates

Let's go back to Stijn's simple try...

Age	Trt	Y	Y^1	$\hat{P}^1$	Y^0	$\hat{P}^0$
40	1	1	1	0.8	?	0.7
50	1	0	0	0.6	?	0.55
60	1	1	1	0.7	?	0.6
50	0	0	?	0.7	0	0.6
30	0	1	?	0.6	1	0.5
40	0	0	?	0.5	0	0.45

- By randomization: fine to compare outcomes of treated with outcomes of untreated

Potential of baseline covariates

Let's go back to Stijn's simple try. . .

Age	Trt	Y	Y^1	$\hat{P}^1$	Y^0	$\hat{P}^0$
40	1	1	1	0.8	?	0.7
50	1	0	0	0.6	?	0.55
60	1	1	1	0.7	?	0.6
50	0	0	?	0.7	0	0.6
30	0	1	?	0.6	1	0.5
40	0	0	?	0.5	0	0.45

- By randomization: fine to compare outcomes of treated with outcomes of untreated
- Based on baseline covariates (e.g., age): guesses about what outcome would be for all participants if they were (un)treated

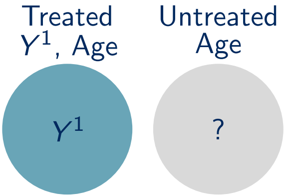
Covariate Adjusted Estimator

Example: $E(Y^1)$

Treated	Untreated
Y^1, Age	Age

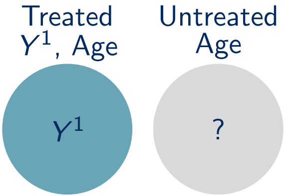
Covariate Adjusted Estimator

Example: $E(Y^1)$



Covariate Adjusted Estimator

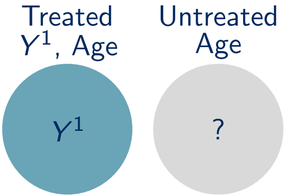
Example: $E(Y^1)$



Estimator for $E(Y^1)$ is obtained by

Covariate Adjusted Estimator

Example: $E(Y^1)$

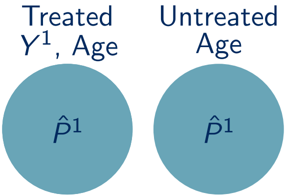


Estimator for $E(Y^1)$ is obtained by

- fitting a logistic regression model for outcome Y given age among the treated patients,

Covariate Adjusted Estimator

Example: $E(Y^1)$

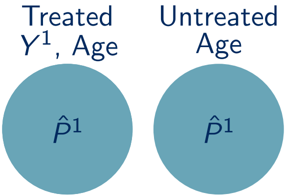


Estimator for $E(Y^1)$ is obtained by

- fitting a logistic regression model for outcome Y given age among the treated patients,
- using this model to impute outcome for **all** patients,

Covariate Adjusted Estimator

Example: $E(Y^1)$



Estimator for $E(Y^1)$ is obtained by

- fitting a logistic regression model for outcome Y given age among the treated patients,
- using this model to impute outcome for **all** patients,
- taking the average of imputed outcomes

Some Advantages

- Similar for an estimate of population disease risk on control
  - We can then contrast these estimates as differences, ratios, . . .

Some Advantages

- Similar for an estimate of population disease risk on control
  - We can then contrast these estimates as differences, ratios, ...
- Focus on marginal treatment effect leads to a simple interpretation
  Same as comparing sample averages

Some Advantages

- Similar for an estimate of population disease risk on control
  - We can then contrast these estimates as differences, ratios, ...
- Focus on marginal treatment effect leads to a simple interpretation

  Same as comparing sample averages
- More efficient than standard sample averages if age is predictive for outcome

Simulation Results

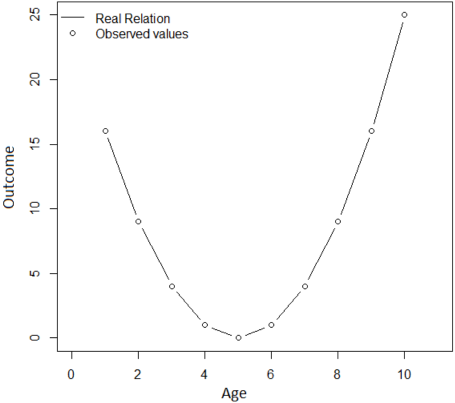
Results for binary outcome and risk difference under correctly specified models

n	Effect	Estimator type	Bias	Power	MSE	RE
100	-0.201	Unadj.	0.025	0.463	0.829	1.000
		Adj.	0.023	0.607	0.755	0.911
200	-0.201	Unadj.	0.010	0.821	0.864	1.000
		Adj.	-0.001	0.895	0.749	0.867
500	-0.126	Unadj.	-0.013	0.798	0.979	1.000
		Adj.	-0.007	0.862	0.850	0.868
1000	-0.091	Unadj.	0.012	0.837	0.898	1.000
		Adj.	0.020	0.892	0.817	0.910

Results from Benkeser, et al. (2020) "Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes." Biometrics.

What if models are misspecified?

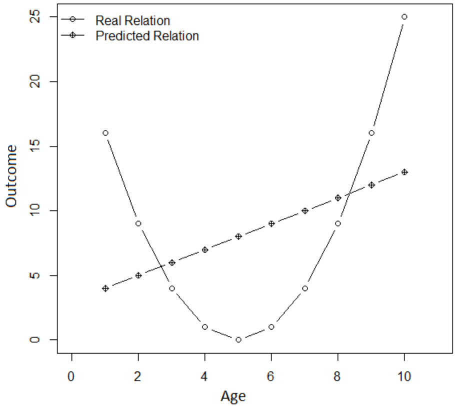
What if relationship between age and outcome in treated patients is not linear...



For simplicity, the outcome is continuous now

What if models are misspecified?

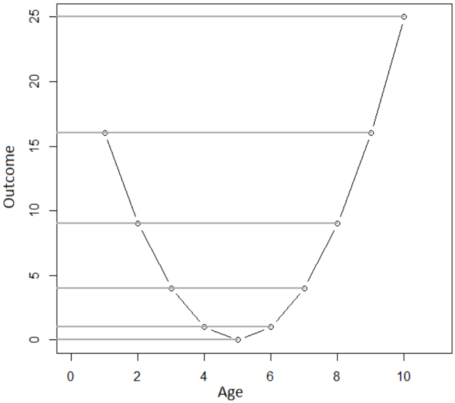
..., but we fit a misspecified model *outcome* $\sim$ *age*?



For simplicity, the outcome is continuous now

What if models are misspecified?

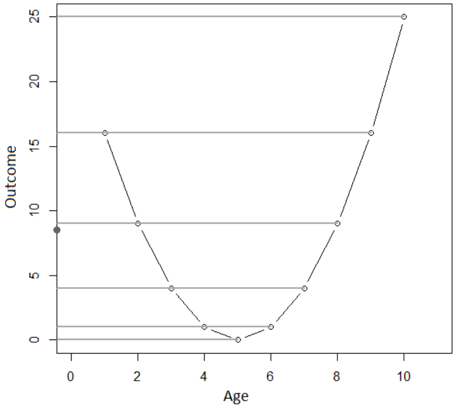
Projections of the observed outcomes on the y-axis,



For simplicity, the outcome is continuous now

What if models are misspecified?

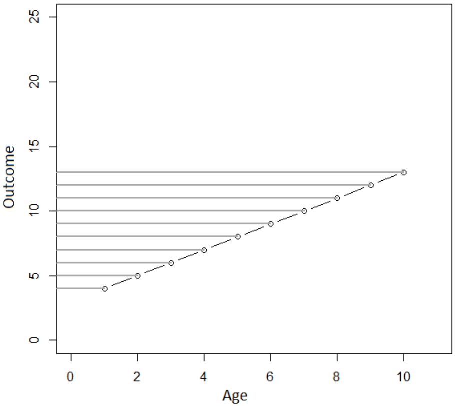
average to 8.5.



For simplicity, the outcome is continuous now

What if models are misspecified?

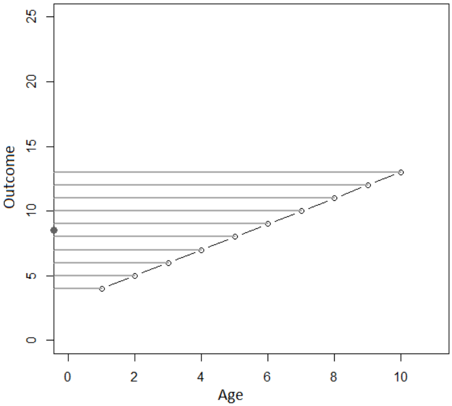
Projections of the predictions on the y-axis,



For simplicity, the outcome is continuous now

What if models are misspecified?

also average to 8.5.



For simplicity, the outcome is continuous now

What if models are misspecified?

- In treatment arm: mean of predictions (under treatment) $=$ mean of observed outcomes, regardless of whether your model is correct or not

What if models are misspecified?

- In treatment arm: mean of predictions (under treatment) = mean of observed outcomes, regardless of whether your model is correct or not
- Under randomization, this robustness against misspecification also holds for mean of predictions (under treatment) for **all** patients

What if models are misspecified?

- In treatment arm: mean of predictions (under treatment) = mean of observed outcomes, regardless of whether your model is correct or not

- Under randomization, this robustness against misspecification also holds for mean of predictions (under treatment) for **all** patients

$\Rightarrow$ Consistent estimator for $E(Y^1)$, even when model is wrong.

Potential of baseline covariates

Mean of predictions based on glm's with canonical link and intercept, fitted in both arms separately

- Asymptotically unbiased estimator, even when outcome regression model is wrong (**robustness**)
  - They overcome the concern as to whether covariate adjustment (and possible misspecification of the model) is appropriate in randomized experiments.

Potential of baseline covariates

Mean of predictions based on glm's with canonical link and intercept, fitted in both arms separately

- Asymptotically unbiased estimator, even when outcome regression model is wrong (**robustness**)
  - They overcome the concern as to whether covariate adjustment (and possible misspecification of the model) is appropriate in randomized experiments.
- Model misspecification may reduce efficiency, but (almost) never outperformed by the standard analyses (**more efficient**).

Inference

- Standard errors easy to calculate
  - Can be done with 1 line of code
  - Take into account uncertainty in imputations
  - Similar to variance of sample mean

Inference

- Standard errors easy to calculate
  - Can be done with 1 line of code
  - Take into account uncertainty in imputations
  - Similar to variance of sample mean
- and are valid even when the model is misspecied (Vermeulen and Vansteelandt, 2015)

Inference

- Standard errors easy to calculate
  - Can be done with 1 line of code
  - Take into account uncertainty in imputations
  - Similar to variance of sample mean
- and are valid even when the model is misspecied (Vermeulen and Vansteelandt, 2015)
- or when variable selection is used (Avagyan and Vansteelandt, 2021).

Recommendations to Pharma: Gaining Precision

- Efficiency can be gained by making explicit use of comparable groups, without risk of bias.

Recommendations to Pharma: Gaining Precision

- Efficiency can be gained by making explicit use of comparable groups, without risk of bias.
- Use of baseline covariates raises concerns due to multicollinearity, measurement error, missing data, ...
  - All easily addressed without inflating risk of bias.

Recommendations to Pharma: Gaining Precision

- Efficiency can be gained by making explicit use of comparable groups, without risk of bias.
- Use of baseline covariates raises concerns due to multicollinearity, measurement error, missing data, . . .
    - All easily addressed without inflating risk of bias.
- Use of models raises concerns regarding model building and variable selection.
    - Also does not inflate risk of bias when using a pre-specified algorithm on a pre-specified list of candidate variables.

Recommendations to Pharma: Gaining Precision

- Efficiency can be gained by making explicit use of comparable groups, without risk of bias.
- Use of baseline covariates raises concerns due to multicollinearity, measurement error, missing data, . . .
  - All easily addressed without inflating risk of bias.
- Use of models raises concerns regarding model building and variable selection.
  - Also does not inflate risk of bias when using a pre-specified algorithm on a pre-specified list of candidate variables.
- Main effect models will often suffice; even machine learning can be used, which is particularly useful in more complex settings. (see talk Alex Luedtke)

Plan

1 Improving Efficiency of Final Analysis

2 Improving efficiency of Interim Analysis

Improving efficiency of Interim Analysis

Pharmaceutical Statistics
The Journal of Applied Statistics in the Pharmaceutical Industry
The official journal of PSI

MAIN PAPER

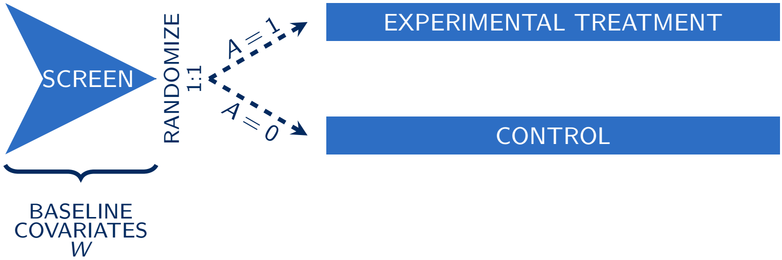
Improving interim decisions in randomized trials by exploiting information on short-term endpoints and prognostic baseline covariates

Kelly Van Lancker, An Vandebosch, Stijn Vansteelandt

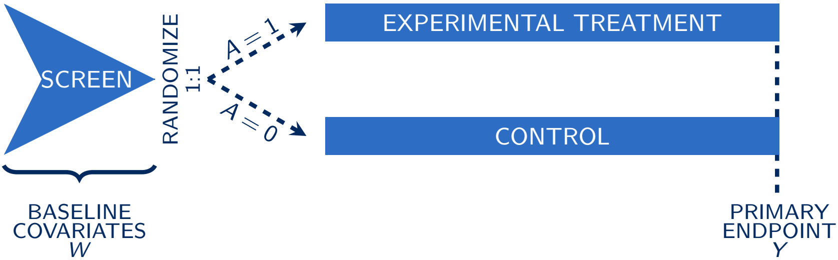
First published: 05 April 2020 | https://doi.org/10.1002/pst.2014 | Citations: 1

Study Design

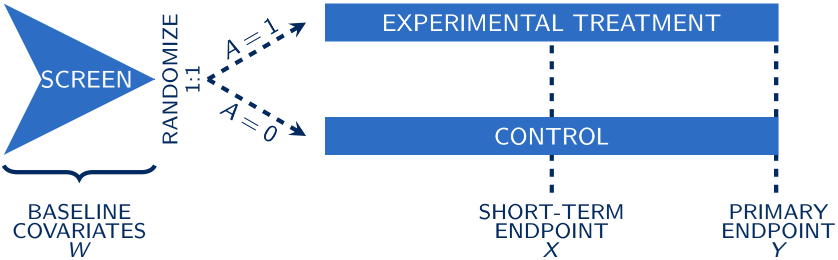
Study Design



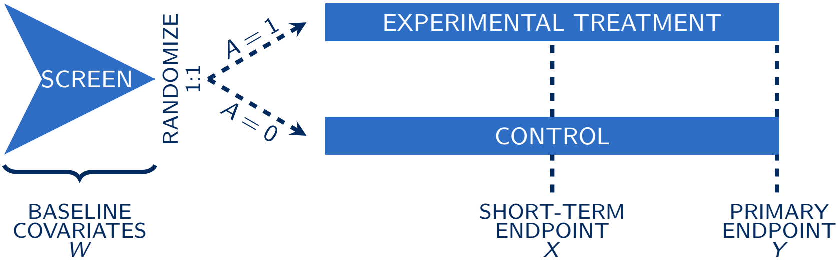
Study Design



Study Design



Study Design

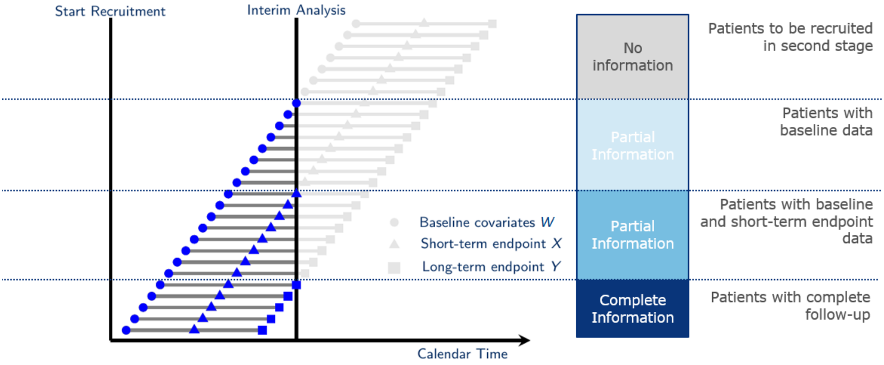


Goal

Define P_j ($j \in \{0, 1\}$) as probability of successful primary outcome;

$$H_0 : P_1 = P_0 \text{ vs } H_A : P_1 > P_0.$$

Study Design



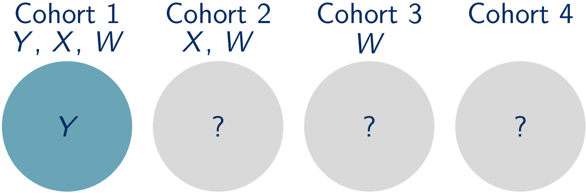
Interim Estimator

Cohort 1	Cohort 2	Cohort 3	Cohort 4
Y, X, W	X, W	W	

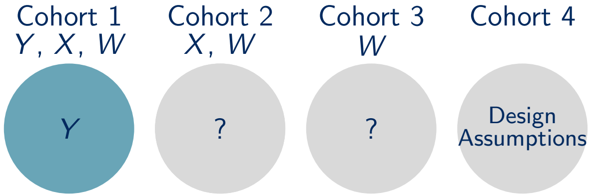
Interim Estimator

Cohort 1	Cohort 2	Cohort 3	Cohort 4
Y, X, W	X, W	W	

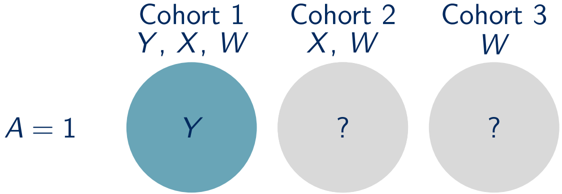
Interim Estimator



Interim Estimator

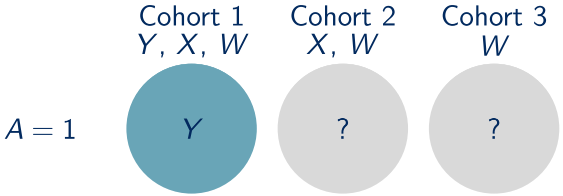


Interim Estimator



Estimator for P_1 is obtained by

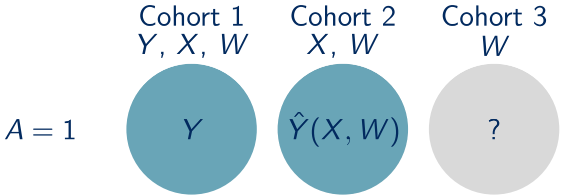
Interim Estimator



Estimator for P_1 is obtained by

1. fitting a regression model for outcome Y given short-term endpoint X and baseline covariates W among the treated patients in cohort 1,

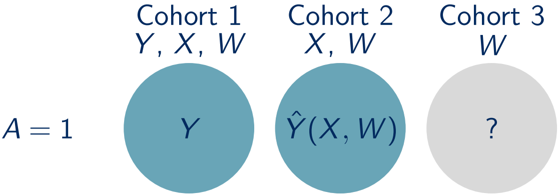
Interim Estimator



Estimator for P_1 is obtained by

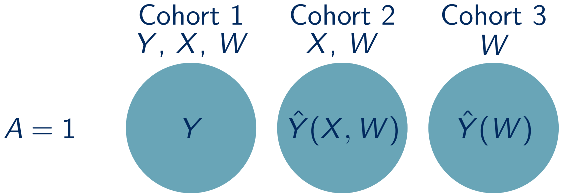
1. fitting a regression model for outcome Y given short-term endpoint X and baseline covariates W among the treated patients in cohort 1,
2. using this model to impute outcome Y for the treated patients in cohort 2,

Interim Estimator



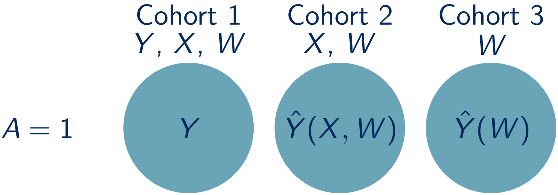
3. regressing (imputed) outcome Y on the baseline covariates W in the imputed dataset (cohort 1 and 2),

Interim Estimator



3. regressing (imputed) outcome Y on the baseline covariates W in the imputed dataset (cohort 1 and 2),
4. using this model to impute outcome Y for the treated patients in cohort 3, and

Interim Estimator



3. regressing (imputed) outcome Y on the baseline covariates W in the imputed dataset (cohort 1 and 2),
4. using this model to impute outcome Y for the treated patients in cohort 3, and
5. taking the average of observed and imputed outcomes Y $(= \hat{P}_1^{interim})$.

Interim Estimator

Under random recruitment,

- model misspecification does not introduce bias (**robustness**),
- but may reduce efficiency.
- Despite the precision loss, (almost) never outperformed by the standard analyses (**more efficient**).

(e.g. Tsiatis, 2006; Qian, Rosenblum and Qiu, submitted 2017)

Interim Test Statistic

Estimator treatment difference:

- $\hat{P}_0^{interim}$: similar reasonings for $A = 0$

  $\Rightarrow \hat{P}_1^{interim} - \hat{P}_0^{interim}$

Interim Test Statistic

Estimator treatment difference:

- $\hat{P}_0^{interim}$: similar reasoning for $A = 0$

  $\Rightarrow \hat{P}_1^{interim} - \hat{P}_0^{interim}$

Asymptotic variance of $\hat{P}_1^{interim} - \hat{P}_0^{interim}$:

- Take into account uncertainty in imputations
  - Normally very complex, very simple here
  - Similar to variance of sample mean

Interim Test Statistic

Estimator treatment difference:

- $\hat{P}_0^{interim}$: similar reasonings for $A = 0$

  $\Rightarrow \hat{P}_1^{interim} - \hat{P}_0^{interim}$

Asymptotic variance of $\hat{P}_1^{interim} - \hat{P}_0^{interim}$:

- Take into account uncertainty in imputations
  - Normally very complex, very simple here
  - Similar to variance of sample mean

Inference:

- Calculate test statistic based on estimator and variance
- Incorporate in interim decision procedure like conditional power

Simulation Study: Conditional Power

Interim Analysis to allow stopping for futility when 50% of information is available

Superiority	Method	# Days	% Recruited	Prob. to Stop	Power Loss
	Proposal, correct	1073	67%	1.1%	0.2%
	Proposal, misspecified (1)	1108	69%	1.1%	0.2%
	Proposal, misspecified (2)	1118	70%	1.0%	0.2%
	Proposal, misspecified (3)	1130	71%	1.0%	0.2%
	Proposal, only X	1133	71%	1.0%	0.2%
	Standard CP (only Y)	1223	77%	0.9%	0.2%
Futility	Method	# Days	% Recruited	Prob. to Stop	
	Proposal, correct	1103	69%	48.5%	
	Proposal, misspecified (1)	1123	70%	48.7%	
	Proposal, misspecified (2)	1131	71%	48.4%	
	Proposal, misspecified (3)	1152	72%	48.3%	
	Proposal, only X	1154	72%	48.4%	
	Standard CP (only Y)	1223	76%	48.7%	

Improving interim analyses

- Enables inclusion of baseline covariates and early read-outs
  - Earlier in time and/or more efficient
  - Protecting type I error (when desired)

Improving interim analyses

- Enables inclusion of baseline covariates and early read-outs
  - Earlier in time and/or more efficient
  - Protecting type I error (when desired)
- General framework
  - Different types of endpoints (binary, continuous, ...)
  - Incorporation of multiple early read-outs
  - Incorporation of baseline covariates

Improving interim analyses

- Enables inclusion of baseline covariates and early read-outs
  - Earlier in time and/or more efficient
  - Protecting type I error (when desired)
- General framework
  - Different types of endpoints (binary, continuous, ...)
  - Incorporation of multiple early read-outs
  - Incorporation of baseline covariates
- Proposal extended to re-assess sample size in adaptive designs

Improving interim analyses

- Enables inclusion of baseline covariates and early read-outs
  - Earlier in time and/or more efficient
  - Protecting type I error (when desired)
- General framework
  - Different types of endpoints (binary, continuous, . . .)
  - Incorporation of multiple early read-outs
  - Incorporation of baseline covariates
- Proposal extended to re-assess sample size in adaptive designs
- Extended to incorporate historical information

Thank you for your attention!

This project has received funding from VLAIO under the Baekeland grant agreement HBC.2017.0219.

Van Lancker et al. (2020), Pharmaceutical Statistics

Asymptotic Variance

Let n' denote number of recruited patients at interim. Then, s^2 can be easily estimated as one over n' times the sample variance of the values

$$
\begin{aligned}
&A_i/\hat{\pi}\left(C_i^Y C_i^X/(\hat{\pi}^Y\hat{\pi}^X)(Y-\hat{Y}_{1i}(X,W))\right.\\
&\left.+\, C_i^X/\hat{\pi}^X(\hat{Y}_{1i}(X,W)-\hat{Y}_{1i}(W))+\hat{Y}_{1i}(\boldsymbol{Z})-\hat{P}_1^{interim}\right)\\
&-(1-A_i)/(1-\hat{\pi})\left(C_i^Y C_i^X/(\hat{\pi}^Y\hat{\pi}^X)(Y-\hat{Y}_{0i}(X,W))\right.\\
&\left.+\, C_i^X/\hat{\pi}^X(\hat{Y}_{0i}(X,W)-\hat{Y}_{0i}(W))+\hat{Y}_{0i}(W)-\hat{P}_0^{interim}\right),
\end{aligned}
$$

with $\hat{\pi}$ the observed randomization probability, $\hat{\pi}^X = \hat{P}(C^X = 1)$ and $\hat{\pi}^Y = \hat{P}(C^Y = 1|C^X = 1)$.