Stop the abuse: A plea for a more principled approach to the analysis of adverse events

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How do we typically analyze «safety» in a clinical trial?

Typical reporting of AEs in a clinical trial

Category	All Adverse Events	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)
Infection*	460 (77.3)	418 (70.0)
Neutropenia	301 (50.6)	269 (45.1)
Infusion-related event†		
Any event	406 (68.2)	349 (58.5)
Antibody-related event	353 (59.3)	292 (48.9)
Tumor lysis syndrome	6 (1.0)	3 (0.5)
Cardiac event‡	78 (13.1)	58 (9.7)
Thrombocytopenia	68 (11.4)	45 (7.5)
Second neoplasm§	43 (7.2)	30 (5.0)
Nonmelanoma skin cancer	18 (3.0)	14 (2.3)
Hematologic event¶	6 (1.0)	0
Other	22 (3.7)	18 (3.0)
Myelodysplastic syndrome	2 (0.3)	0
Gastrointestinal perforation	4 (0.7)	3 (0.5)
Hemorrhagic event	57 (9.6)	62 (10.4)

N Engl J Med 2017;377:1331-44.

DOI: 10.1056/NEJMoa1614598

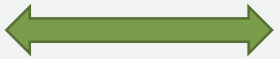
What do these proportions estimate?

- Incidence proportion for a group of patients in interval from 0 to t:

$$\widehat{IP}(t) = \frac{Number\ of\ patients\ with\ AE\ in\ [0,t]}{Total\ number\ of\ patients}.$$

- Estimates probability of AE happening in [0, t] and that **this AE is observed**.
- «this AE is observed»: implies that if we have (administratively) censored patients in our dataset then $\widehat{IP}(t)$ **underestimates true AE probability**.
- Interpretable if all patients have ~ same follow-up.

What do we want to report with safety analyses?

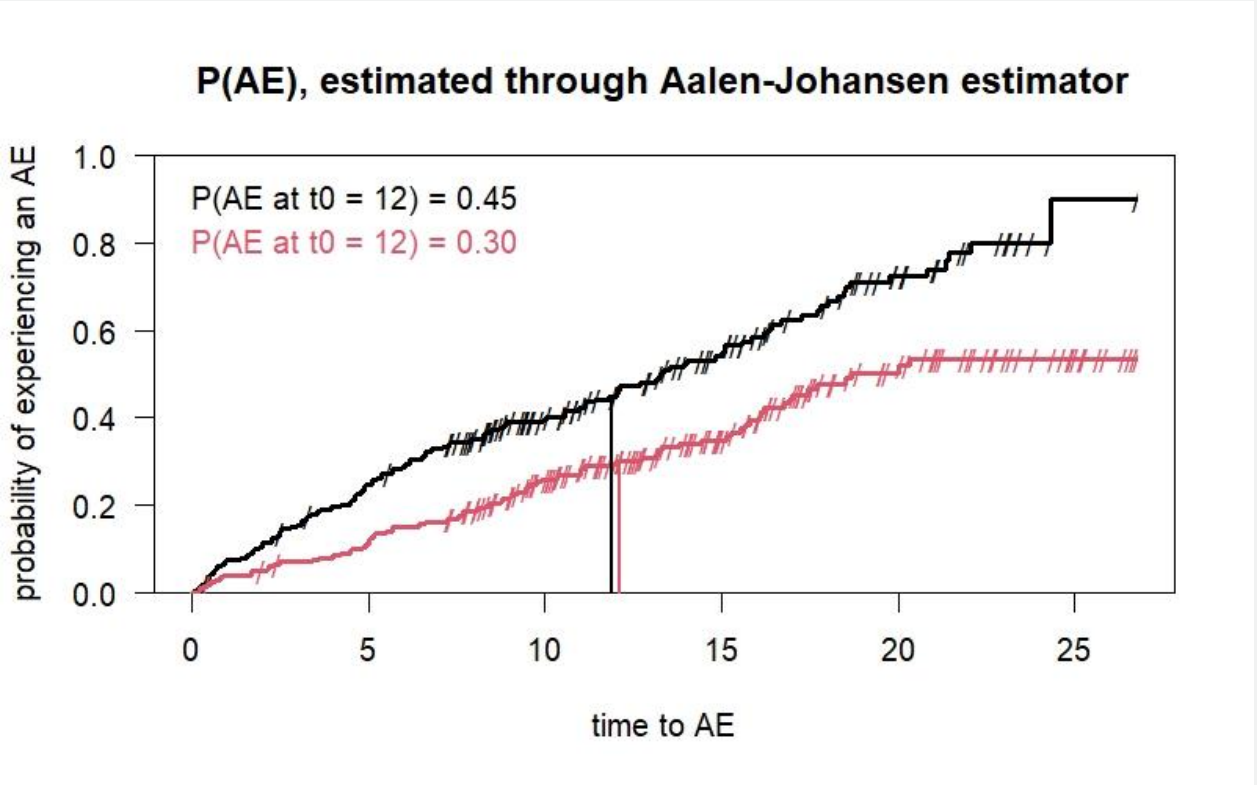
- Signal detection  assessment of AE risk.
- Here: assess AE risk for selected AEs.
- Probability of experiencing an AE, P(AE): **estimand**.

Challenges for assessment of AE risk

- (Administrative) **censoring**: patients not observed on entire [0, t]. Randomized «too late».
- **Competing events**: Clinical events that preclude the occurrence of AE.
  - Death without prior AE.
  - Treatment discontinuation leading to end of AE recording.
  - «Simply censoring» competing events gives biased estimates of probabilities.
- What is the **process that generates the events** (underlying hazard)?

Potential estimators of P(AE)

- Consider «time to AE» → methods from survival analysis.



Can we simply use 1 – Kaplan – Meier?

- For time-to-event endpoints (OS, PFS) we typically use Kaplan-Meier estimates → properly accounts for censoring.
- Do these work also for time to AE?
- Yes – in absence of competing events.
- Competing events: 1 – KM **overestimates** true P(AE).

Potential estimators of AE risk

	Accounts for censoring	Accounts for competing events	Makes no constant hazard assumption
Incidence proportion	**No**	Yes	Yes
1 – Kaplan-Meier	Yes	**No**	Yes
Aalen-Johansen estimator	Yes	Yes	Yes

- **Aalen-Johansen**:
  - Only estimator that accounts for censoring, competing events, and does not make assumption about underlying hazard.
  - Advocated for in statistical literature for decades.
  - «Gold standard». Available in any standard software package.

How large can the bias become in a clinical trial?

SAVVY = academia + pharma

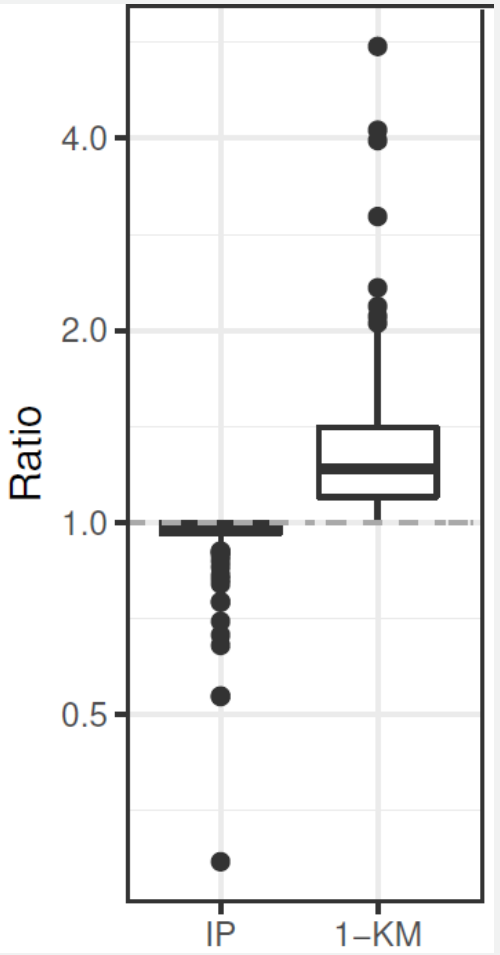
- **S**urvival analysis for **A**d**V**erse events with **V**ar**Y**ing follow-up times (SAVVY):
  - **Collaborative** effort from academia and pharma.
  - Goal: improve analyses of AEs in clinical trials through use **survival techniques** that account for varying follow-up times, censoring and competing events.
- Organizational setup:
  - **Centrally developed** R / SAS macros sent to organizations.
  - Summaries computed on clinical trial datasets within organizations → **raw data never left organization**.
  - Summaries centrally meta-analyzed.

How large can the bias become in a clinical trial?

- Dataset:
  - **Ten** organizations (9 pharma + 1 academic) provided **17 trials** including **186** types of AEs.
  - Trials included between 200 and 7171 patients (median: 443).
- «Gold standard»: Aalen-Johansen estimator of P(AE).
- Maximum follow-up time: compute P(AE) at the last observed AE time.

How large can the bias become in a clinical trial? Incidence proportion (IP)

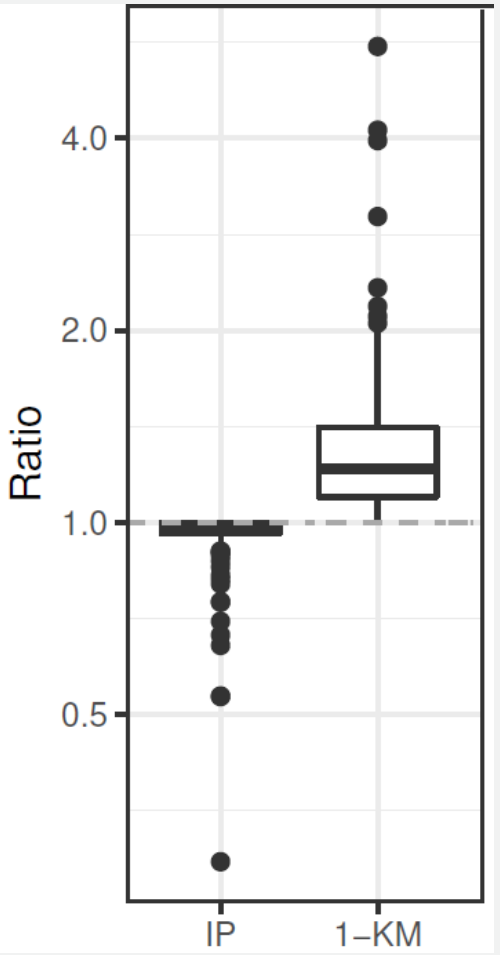
- Every observation in boxplot corresponds to ratio of IP to gold standard for a type of AE.
- Ratio = 1: IP gives same estimate as gold standard.
- **Underestimation of P(AE) up to factor THREE!**
- Overall reasonable performance.
- IP accounts for CEs but not censoring → datasets have many CEs → little censoring.



How large can the bias become in a clinical trial?

I – Kaplan-Meier (I - KM)

- Every observation in boxplot corresponds to ratio of (1 – KM) to gold standard for a type of AE.
- Ratio = 1: (1 – KM) gives same estimate as gold standard.
- **Overestimation of P(AE) up to factor FIVE!**
- (1 – KM) accounts for censoring but not CEs.



Does it impact decisions?

- SmPC frequency categories: very rare (< 0.01%), rare (< 0.1%), uncommon (< 1%), common (< 10%), very common (≥10%).
- Compare frequency category from IP or (1 – KM) to those from gold standard.

Does it impact decisions?

		gold-standard Aalen-Johansen				
		very rare	rare	uncommon	common	very common
incidence proportion	very rare	**6**				
	rare		**0**			
	uncommon			**6**		
	common				**86**	2
	very common					**86**
1-Kaplan-Meier	very rare	**6**				
	rare		**0**			
	uncommon			**4**		
	common			2	**72**	
	very common				14	**88**

- **Potential impact on labeling!**

How about estimation of relative effects?

- Categorization according to German Institute for Quality and Efficiency in Health Care (IQWiG).

		HR Cox for AE			
		(0) no effect	(a) minor	(b) considerable	(c) major
RR gold-standard Aalen-Johansen	(0) no effect	**42**	3	3	1
	(a) minor	9	**2**	1	
	(b) considerable	4	1	**3**	2
	(c) major	2		4	**17**

- **Potential impact on labeling!**

Conclusions

- Start with the **scientific question**: Signal detection? Assessment of AE risk?
- Respect **data structure**: censoring? Competing events?
- Estimand!
- **Select appropriate estimator**.
- Estimation of P(AE) in one cohort: Incidence proportion and (1 – KM) **biased** in presence of censoring or competing events.
- Comparing AE risk between two arms in RCT: differences between estimators become more emphasized.
- Template for:
  - Academia – pharma partnership.
  - Pool results of 17 RCTs without need for individual patient data sharing.

SAVVY: next steps and resources

- Estimate P(AE) in selected indications accounting for data structure.

- Statistical Analyis Plan:
  - Stegherr et al (2021) Biom J https://doi.org/10.1002/bimj.201900347
- Methods:
  - Preprint https://arxiv.org/abs/2001.05709
- Results:
  - One-sample case: https://arxiv.org/abs/2008.07883
  - Two-sample case: https://arxiv.org/abs/2008.07881
- Example R code (markdown file): https://numbersman77.github.io/AEprobs/SAVVY_AEprobs.html

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