Are Estimands Necessary for Time-To-Event Endpoints?

PSI One Day Meeting: Estimands : September 2017

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Roche Biostatistics, Methods, Collaboration & Outreach

with thanks to Colin Neate & Kaspar Rufibach

Are Estimands Necessary for Time-To-Event Endpoints?

Inconsistent Variable Definitions
When is DFS (Disease Free Survival) not DFS?

Table 1. Example of Inconsistent Definitions of Disease-Free Survival

Trial	Local/Regional Recurrence	Distant Metastasis	Death From Any Cause	Invasive Contralateral Breast Cancer	Second Primary Invasive Cancer (nonbreast)	Ipsilateral DCIS	Contralateral DCIS	Ipsilateral LCIS	Contralateral LCIS
BIG 1-98[4]	X	X	X	X	X				
MA-17[1]	X	X		X		X	X	X	X
ATAC[2]	X	X	X	X		X	X		
IES[3]	X	X	X	X					
ARNO[5]	X	X		X					

NOTE: Event-free survival used by ARNO.
Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; BIG, Breast International Group; MA, National Cancer Institute of Canada Clinical Trials Group MA-17; ATAC, Arimidex, Tamoxifen Alone, or in Combination; IES, Intergroup Exemestane 031; ARNO, Arimidex, Nolvadex 95 Study.

*Proposal for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System , JCO, Hudis et al 2007

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Trial objectives and effect quantification may not be aligned.

- **Is the trial measuring what the authors claim to be measuring?**
- **Is the trial measuring what readers of the paper think it is measuring?**

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Inconsistent Variable Definitions
Does It Matter?

PETACC-03 : Colon Cancer Van Cutsem et al. (2005).	
Primary Endpoint : DFS	**Secondary Endpoint : RFS**
Counted second primary cancer other than colon as **event**	Counted second primary cancer other than colon as **not event**
Non-Significant	**Significant**
	This definition was DFS in MOSAIC

Inconsistent Variable Definitions Does It Matter?

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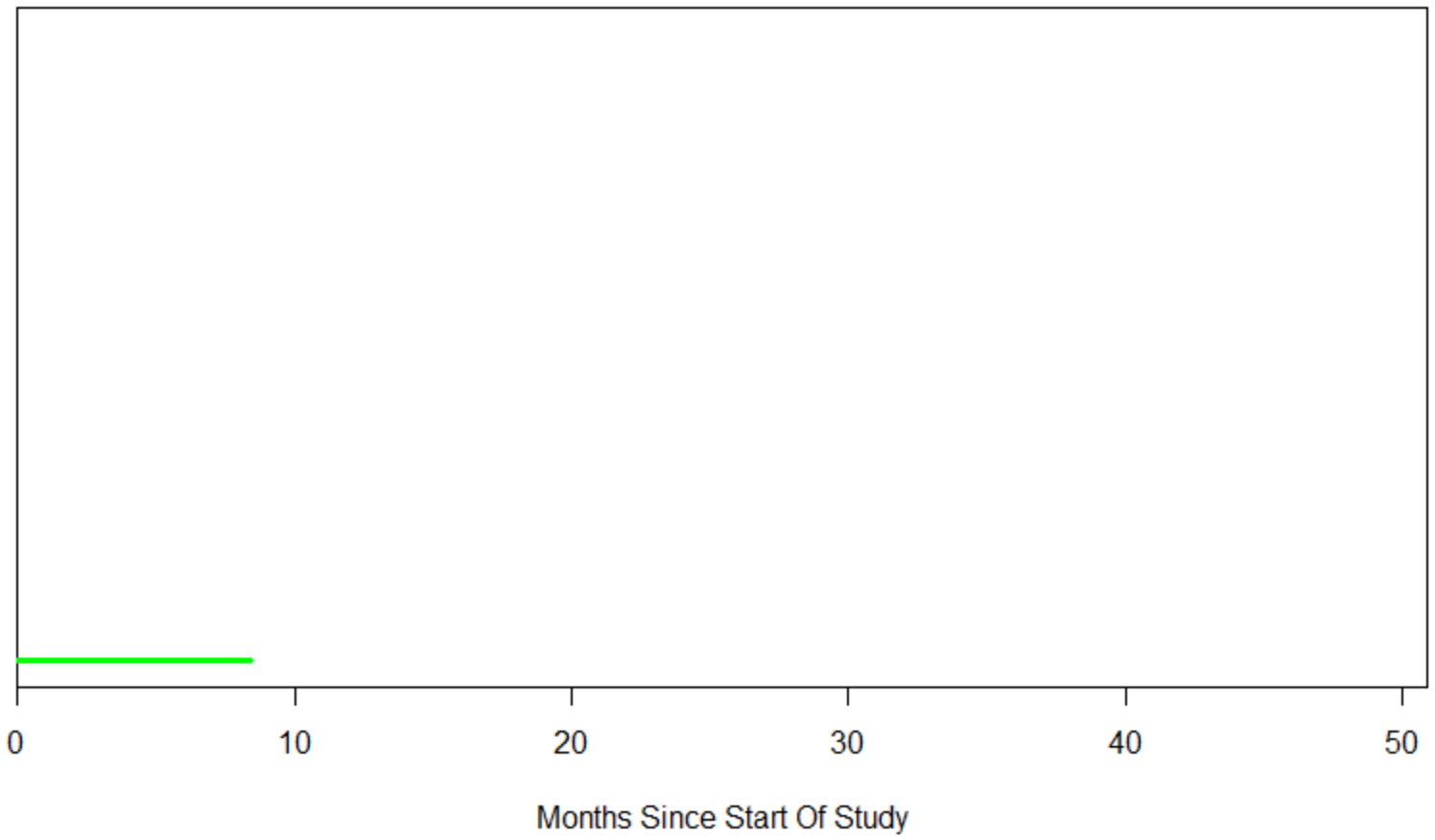
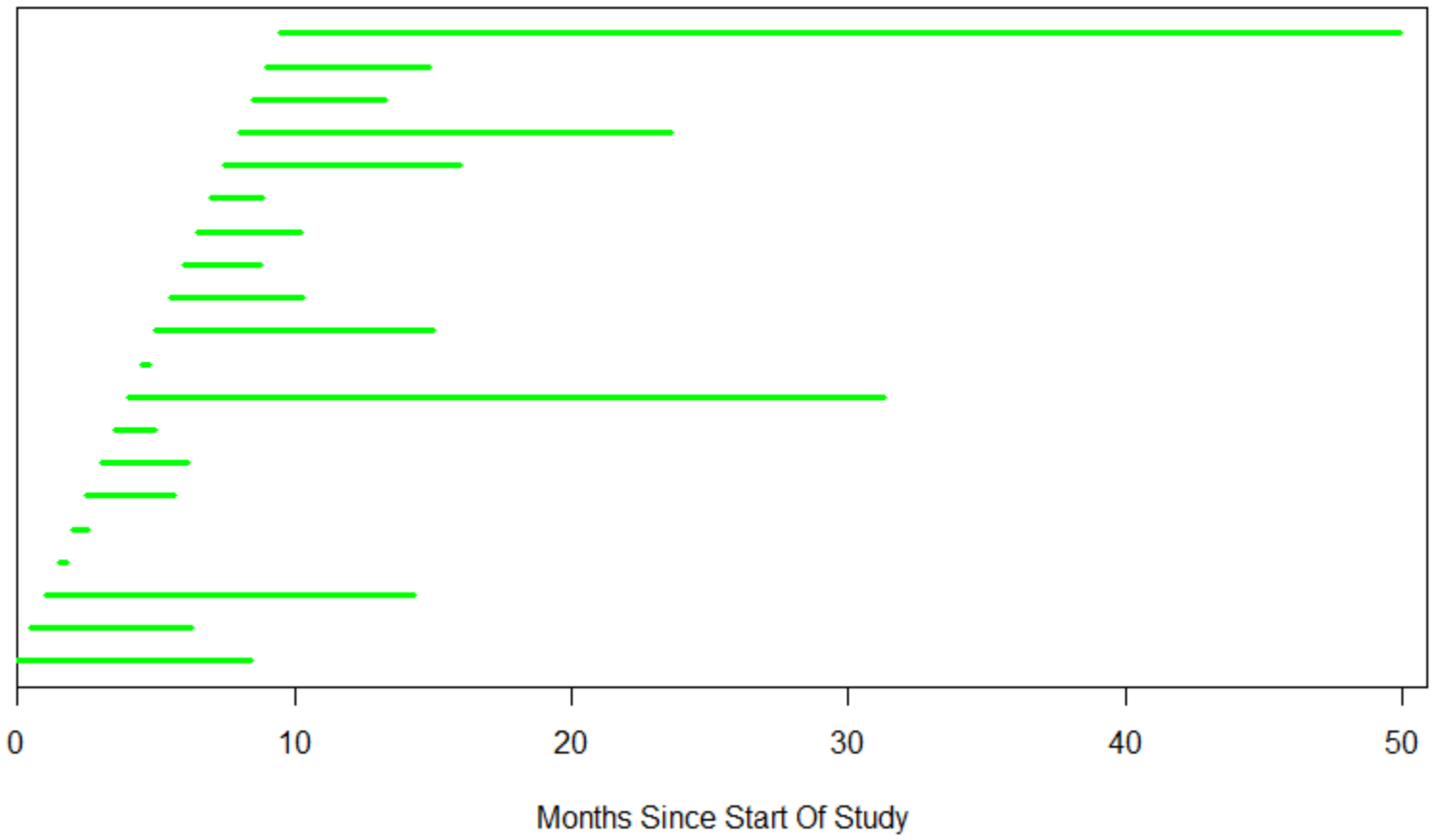
- **Heterogeneous definitions affect both**
  - **Relative (e.g. hazard ratio) and**
  - **Absolute (e.g. milestone survival, medians) measures**
- **Can affect results and interpretation of individual trials**
- **Can have huge impact, when working across trials :**
  - **Bias and/or Variability**
  - **Meta-analysis, Surrogacy analyses, Historical controls.....**

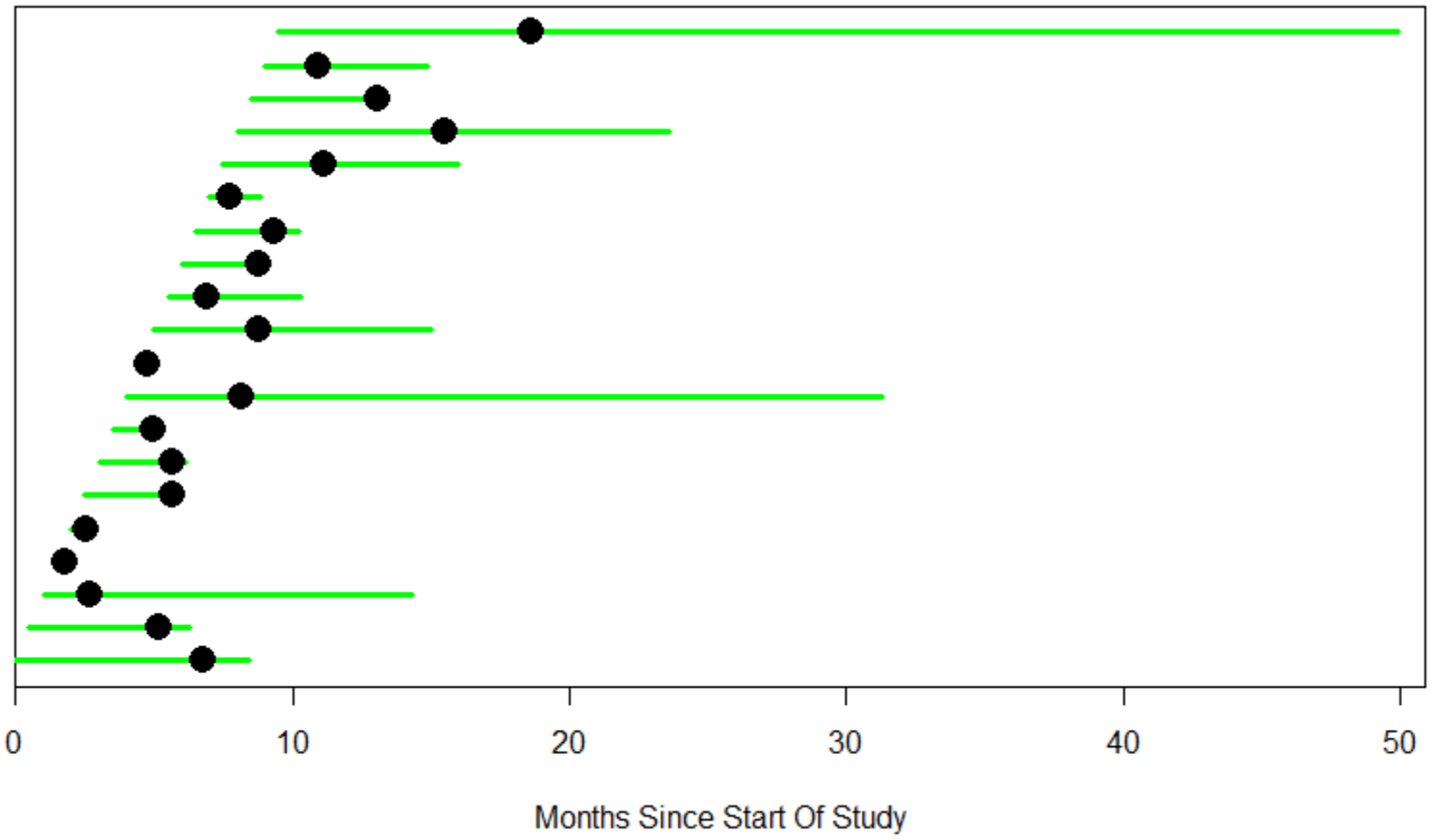
First Patient In An Oncology Trial



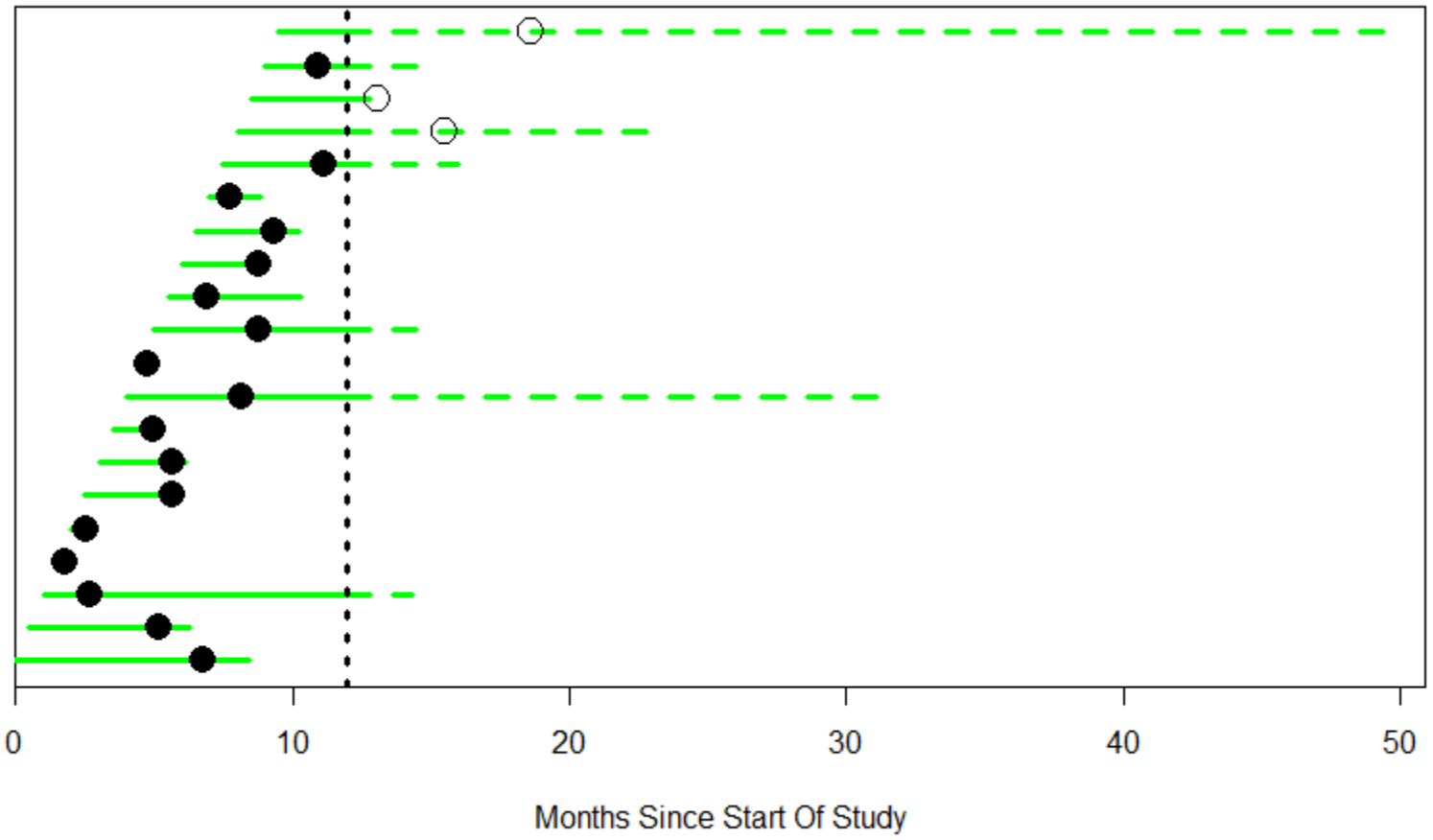
An Oncology Trial



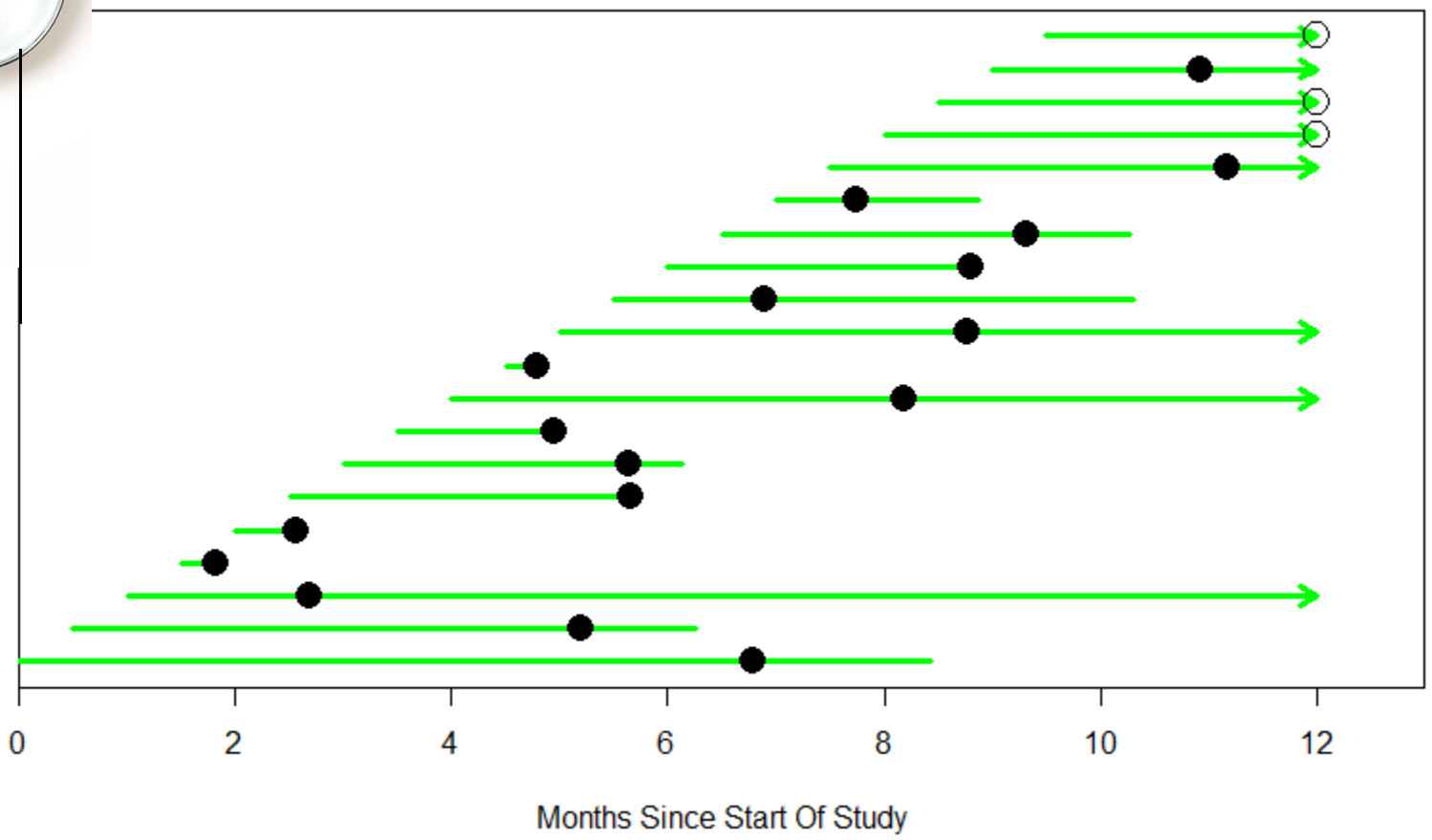
Typically Also Measure An Intermediate Endpoint(s) e.g. PFS , DFS



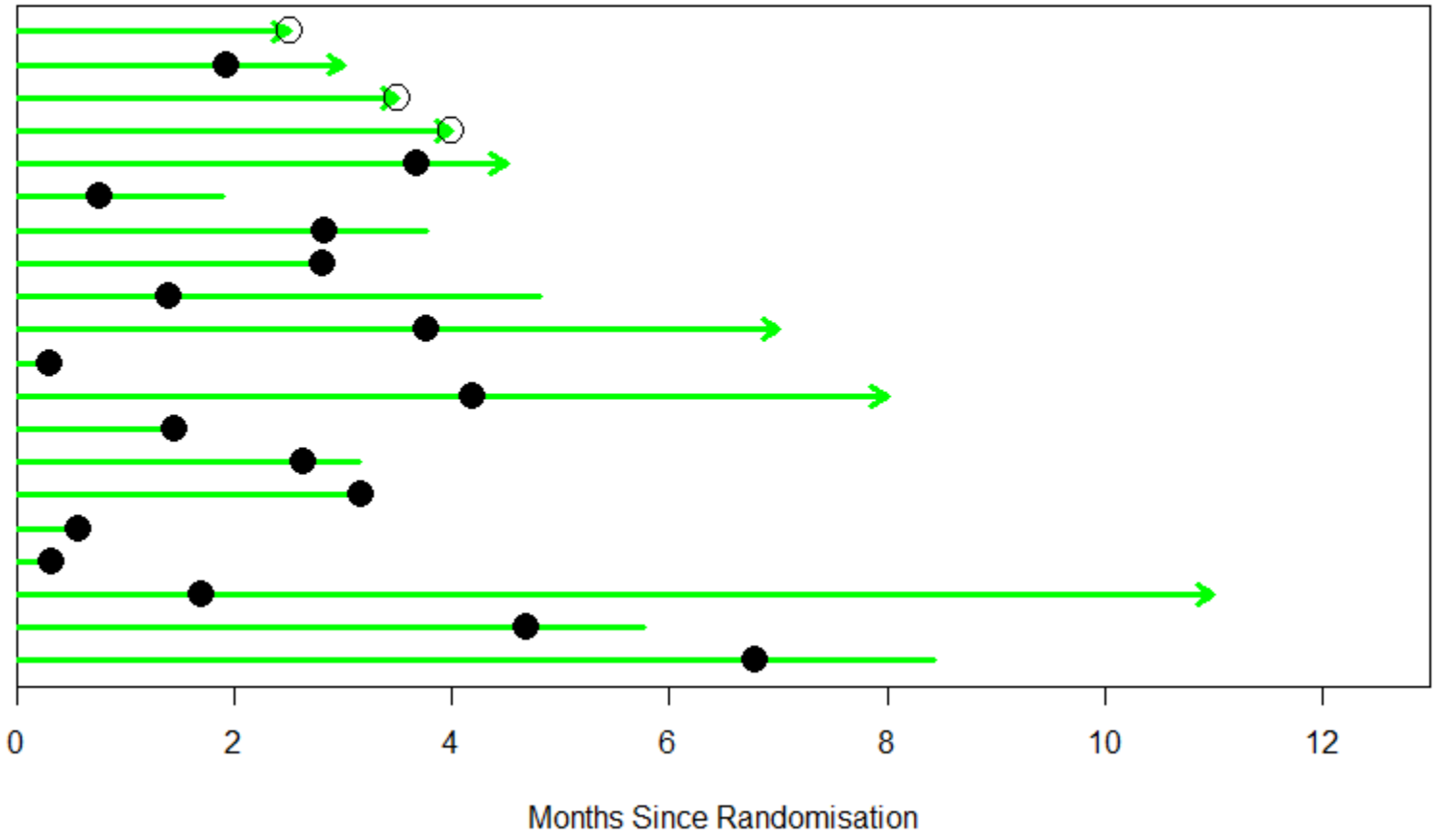
Potential Intercurrent Events 1 : Only Observe Data Up To An Administrative Data Cut-Off -> Censored Data



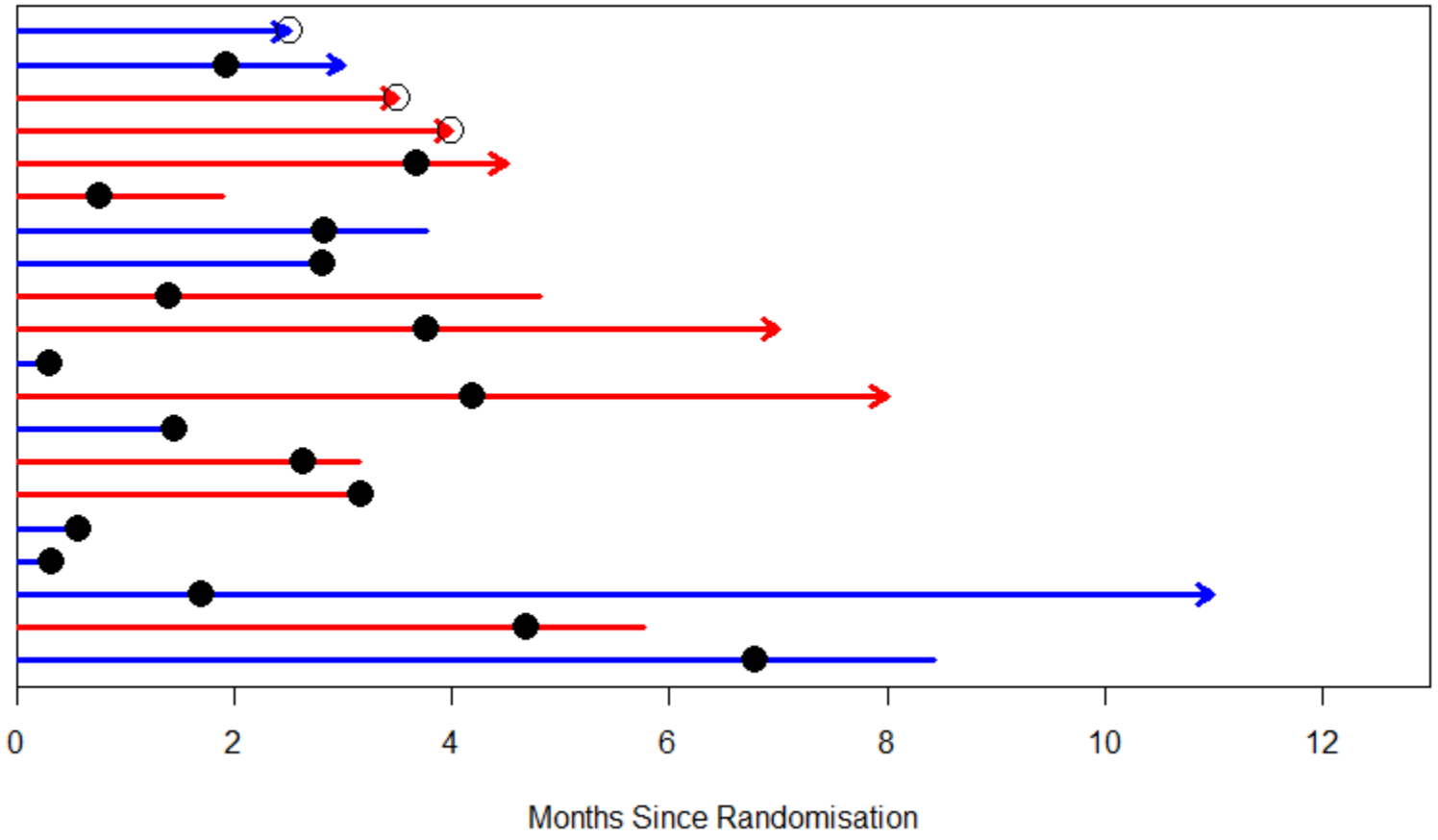
Rescaling To Focus On The Times We Observe



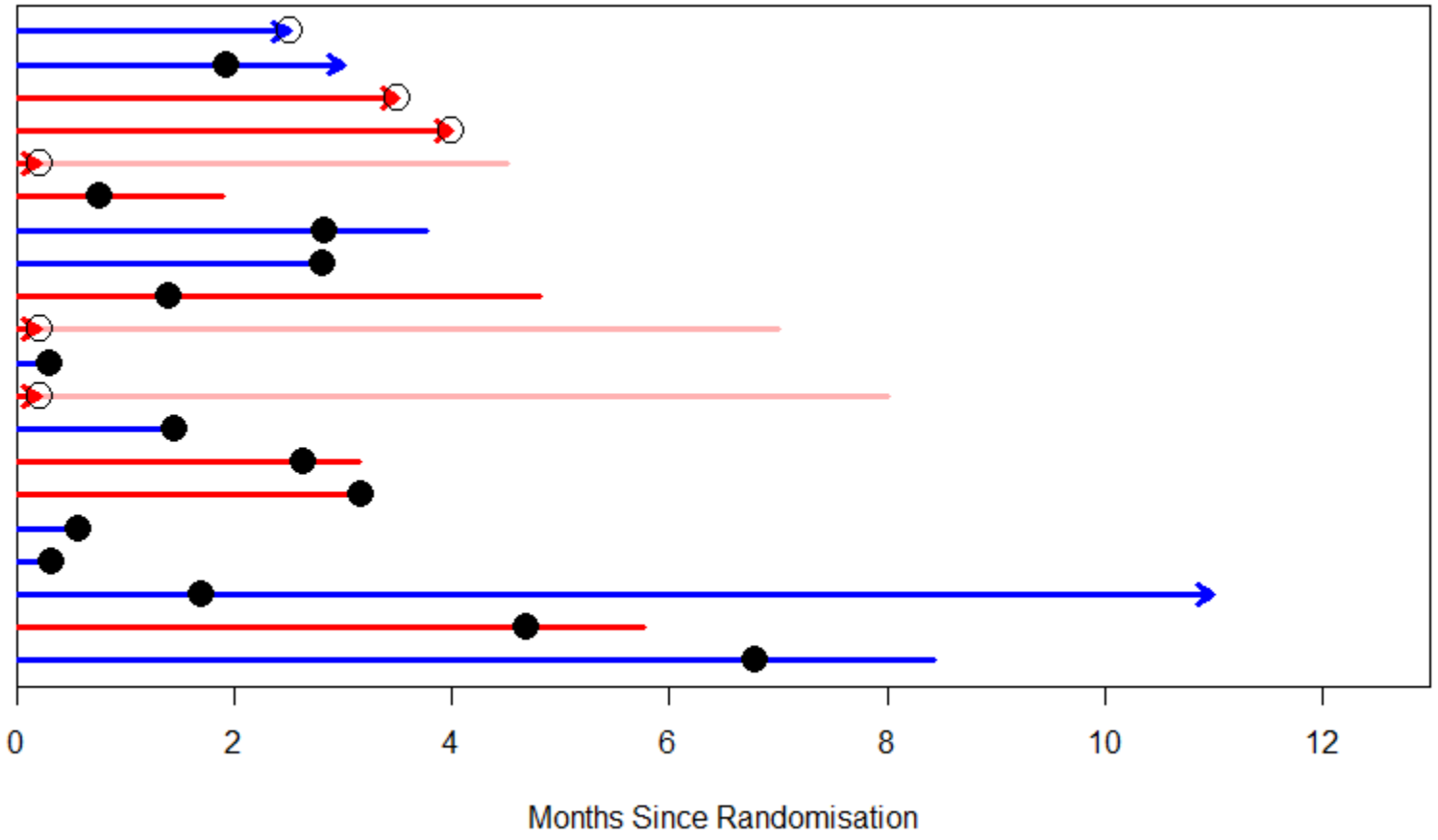
Zeroing Back To A Time Since Randomisation



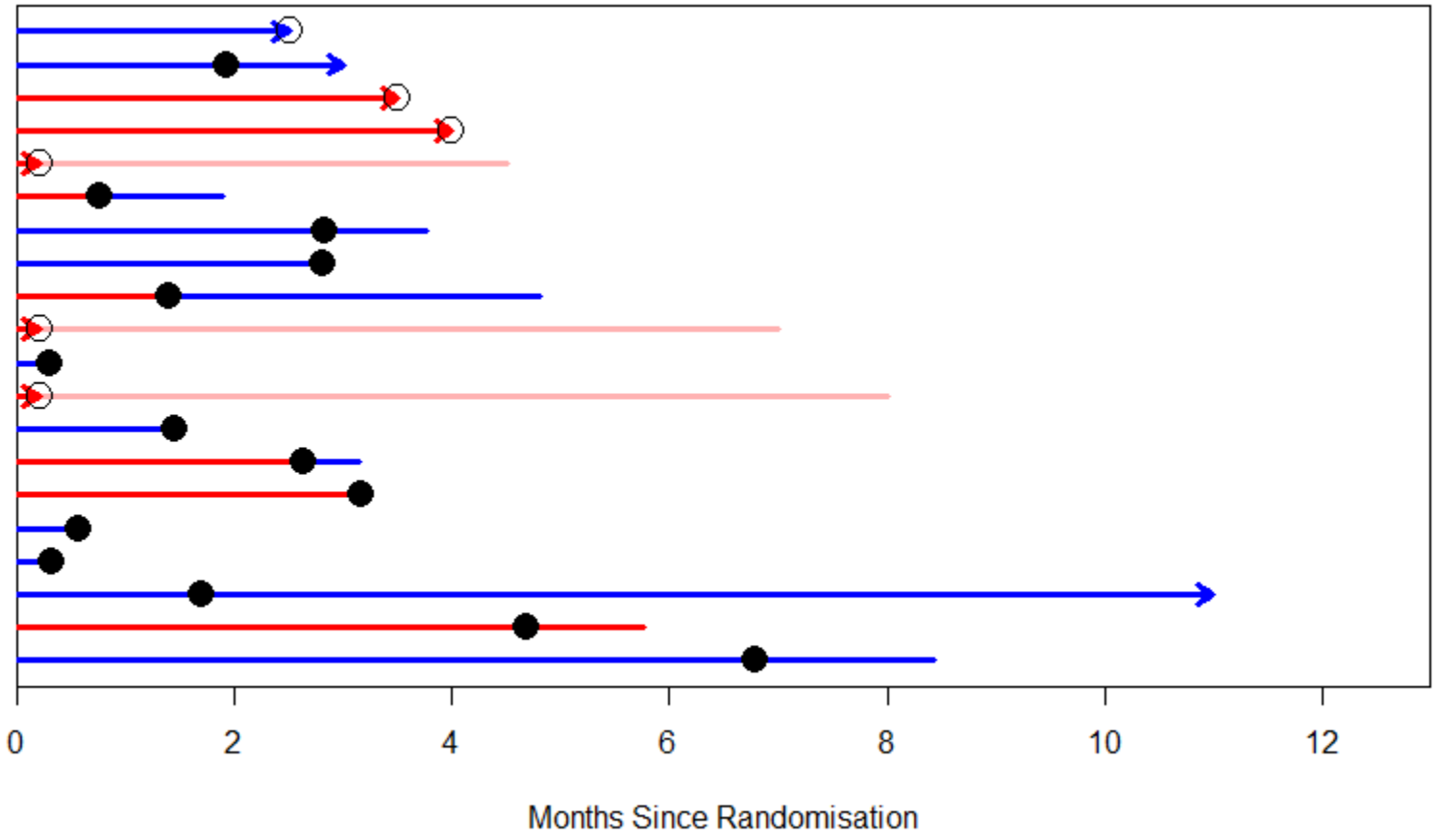
Breaking The Blind



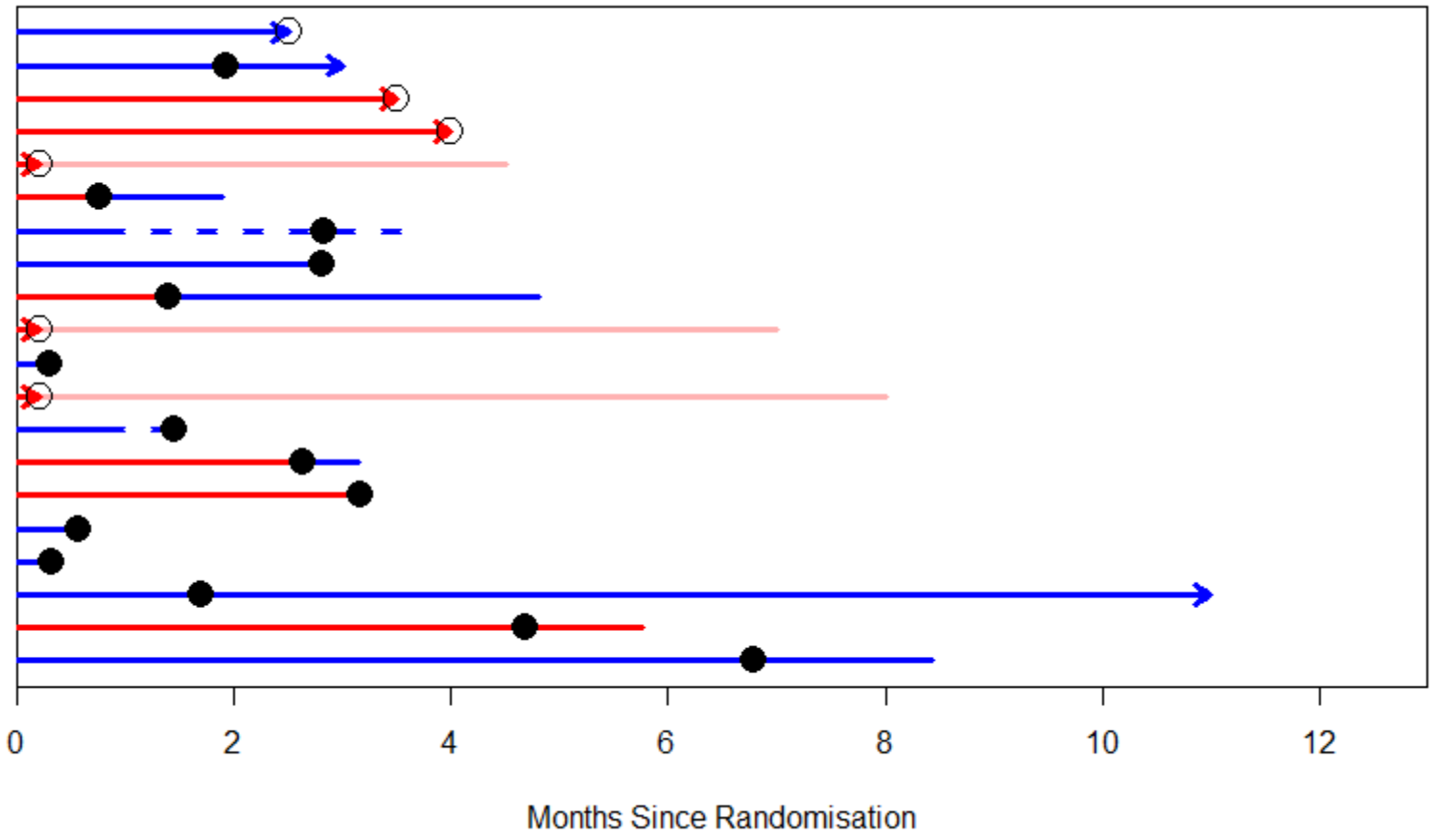
Potential Intercurrent Events 2 : Early Study Withdrawal



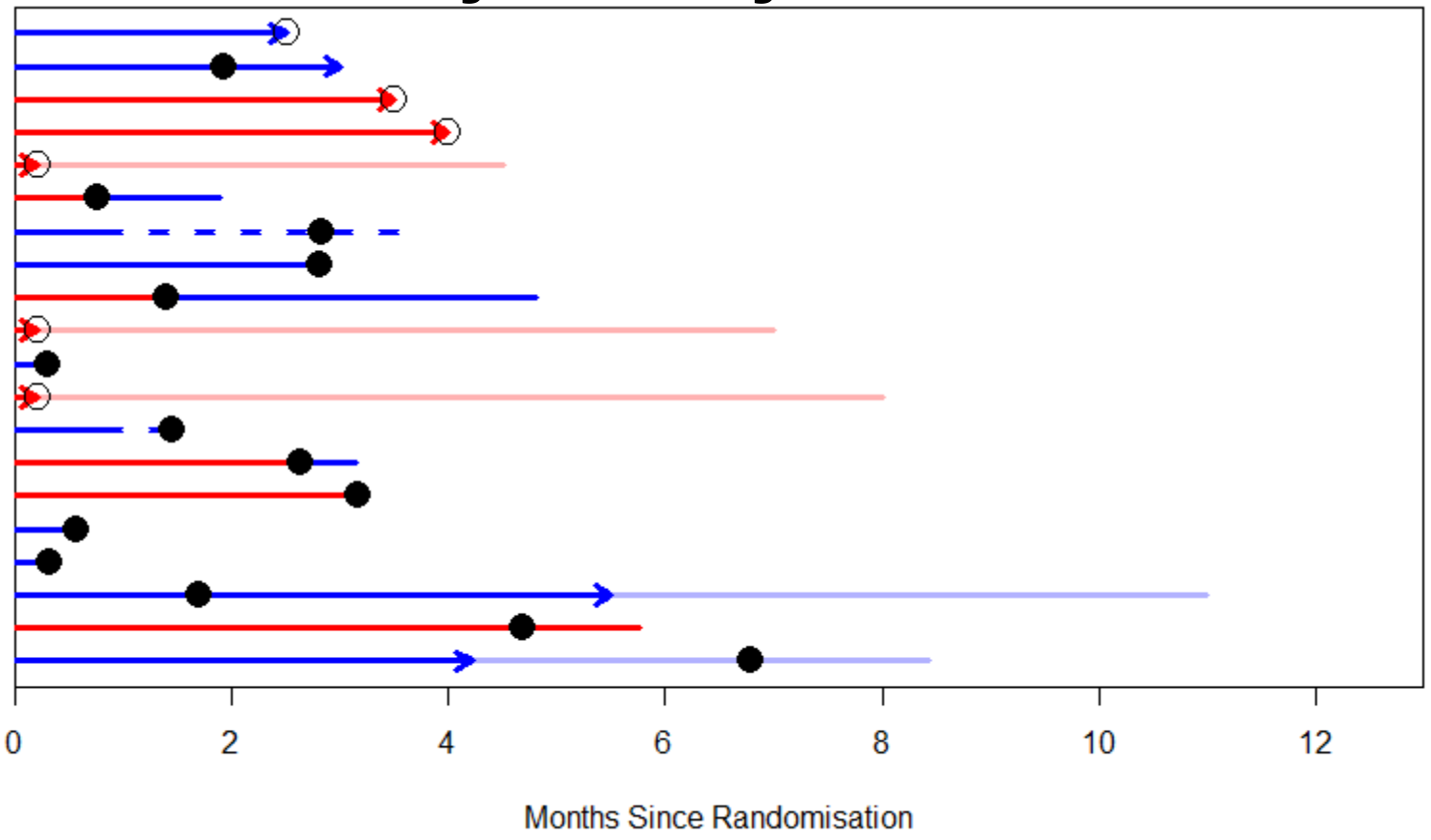
Potential Intercurrent Events 3 : Post Progression Treatment Cross-Over



Potential Intercurrent Events 4 : Dose Reductions



Potential Intercurrent Events 5 :
On-Treatment Withdrawals : May or May Not Be Treatment (Efficacy or Safety) Related



Randomisation is the Gold Standard

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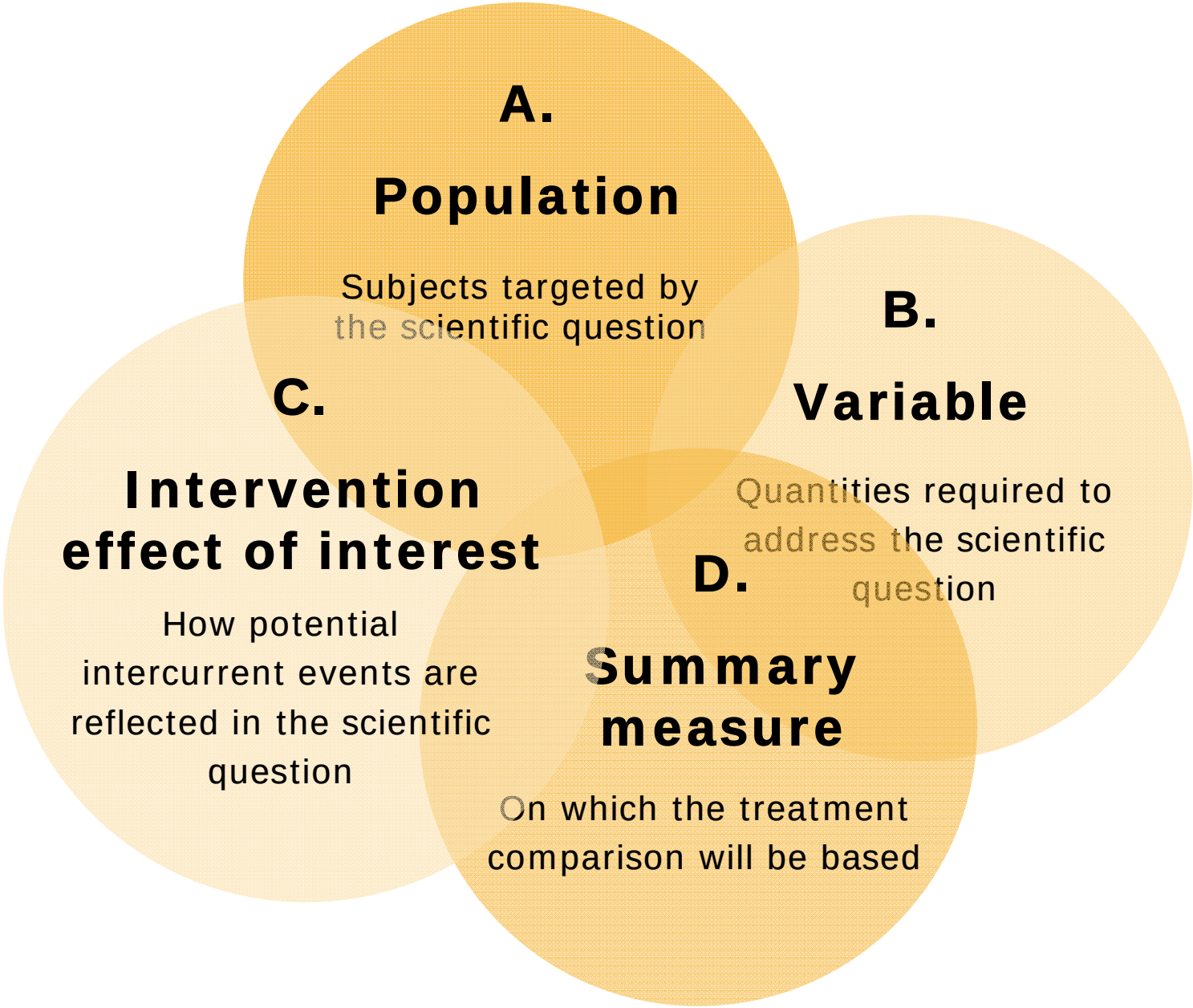
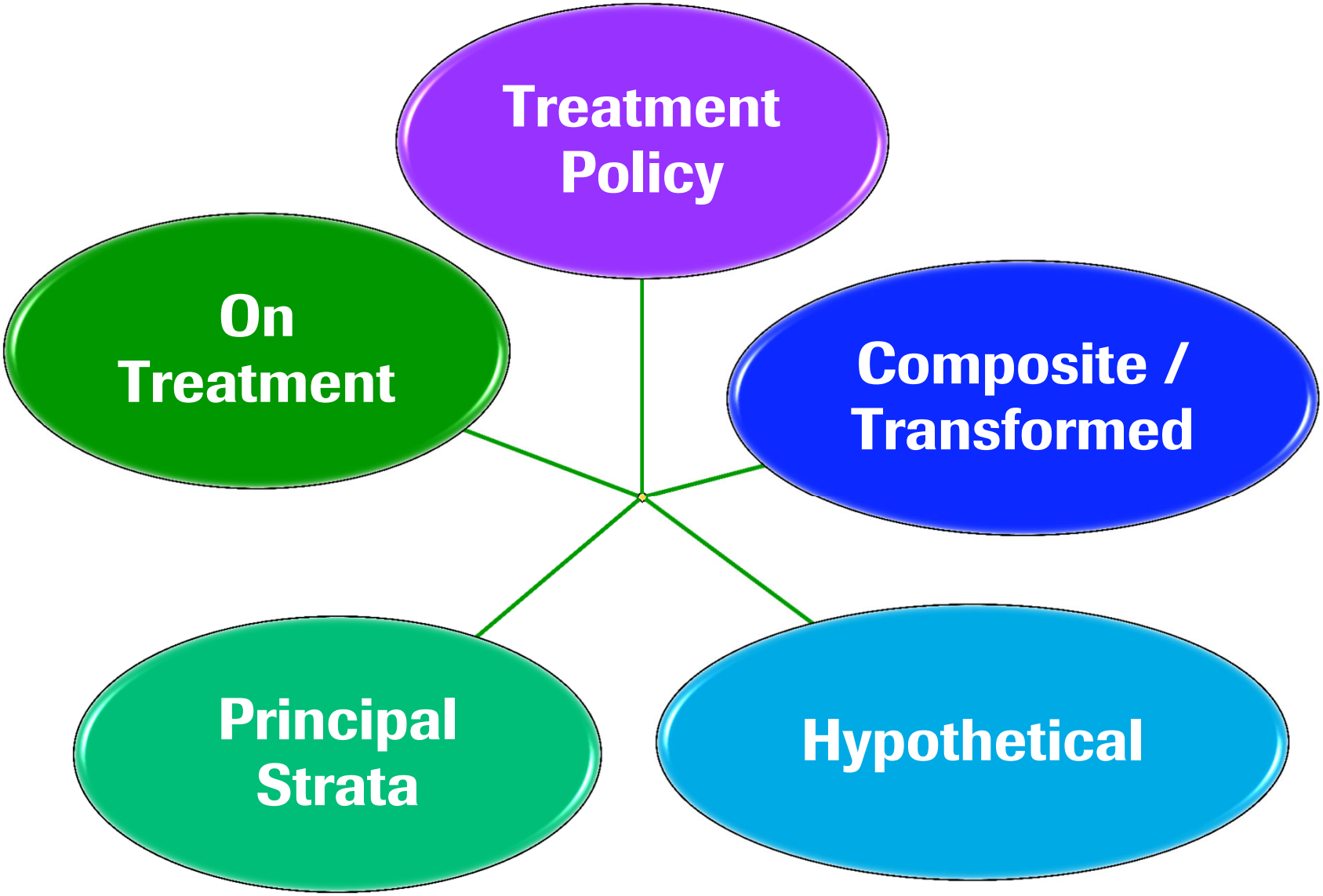
InterCurrent Events make the value of the wealth of information harder to evaluate

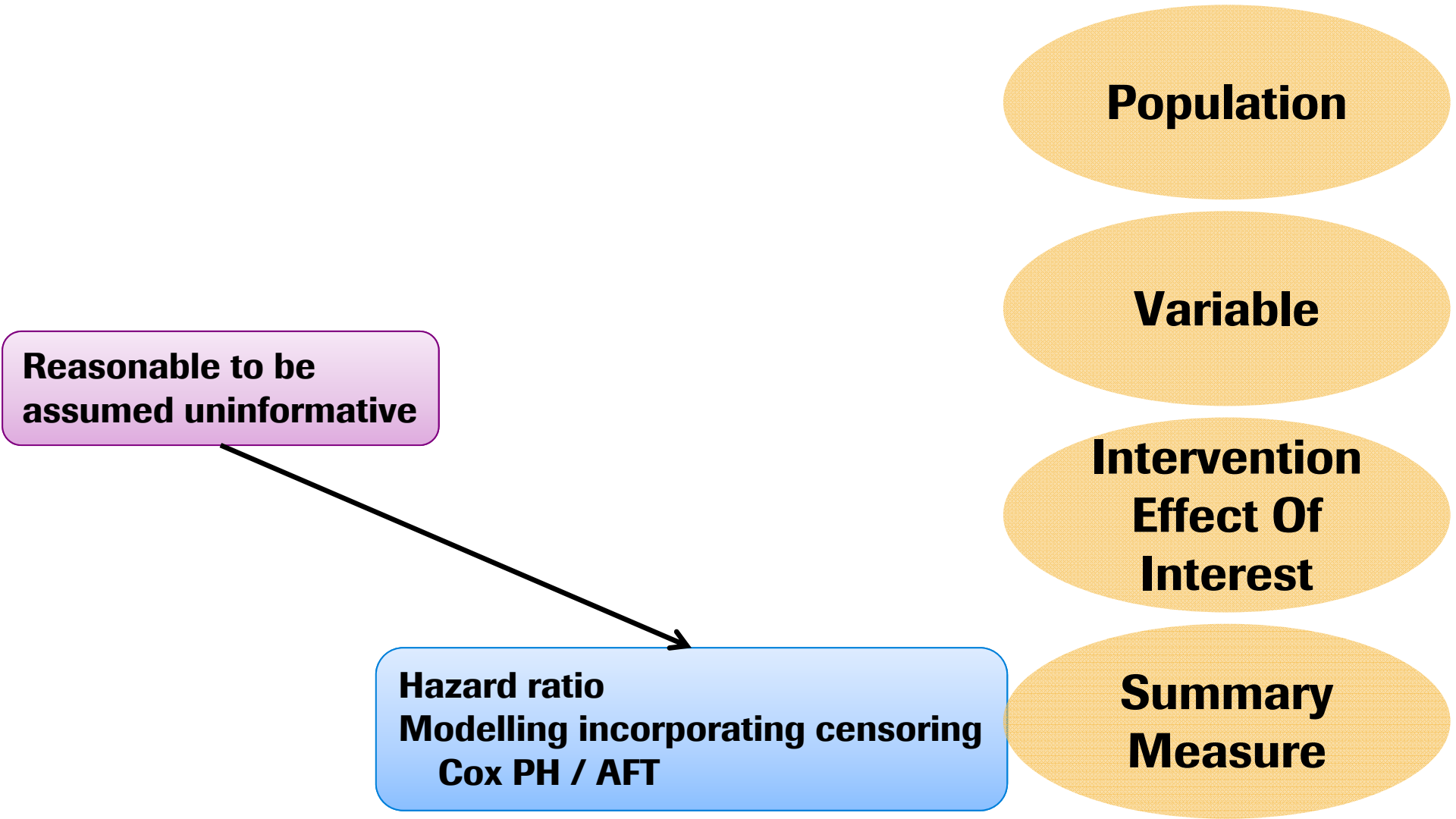
Four Attributes Of An Estimand



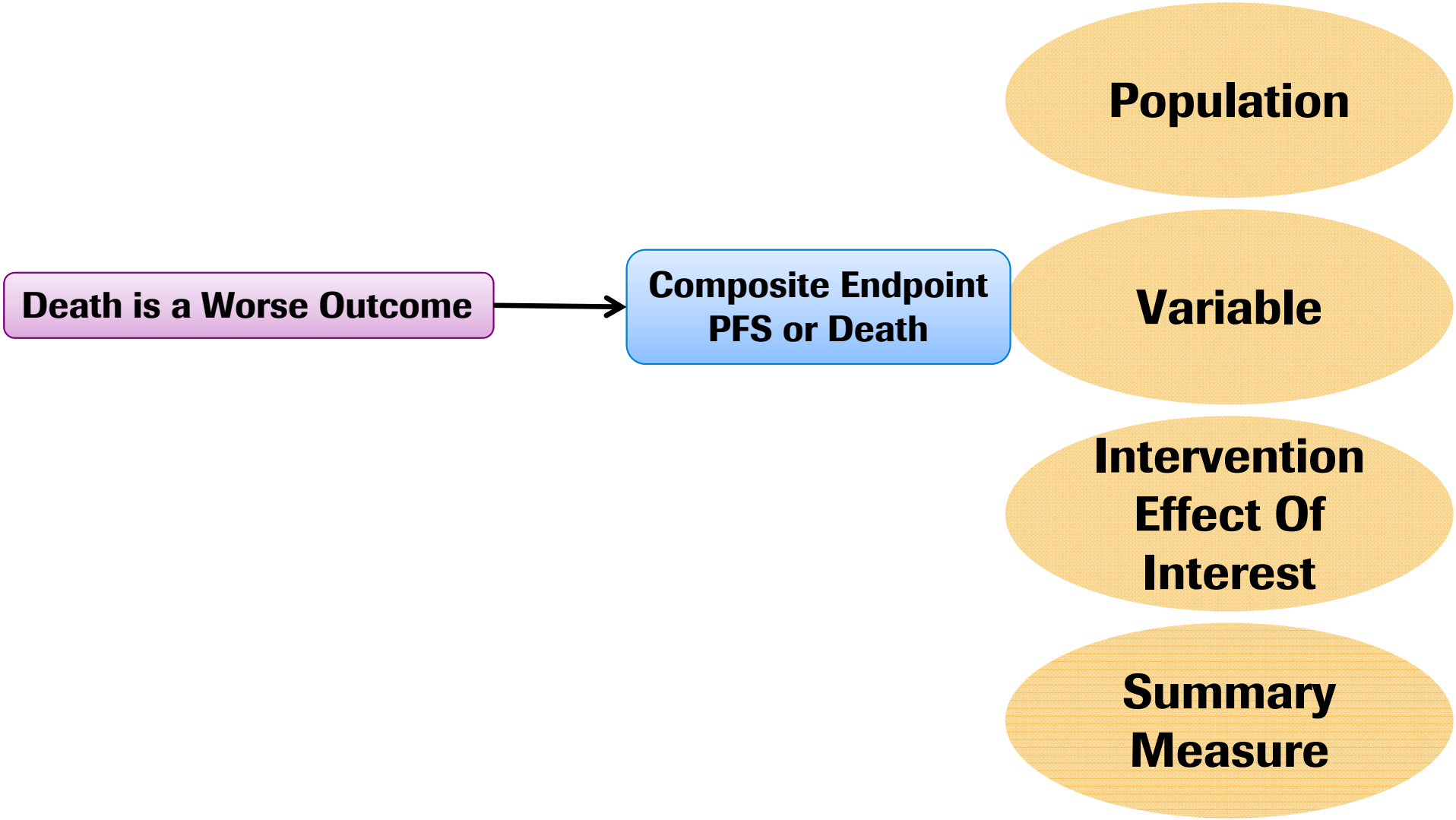
Five Potential Strategies



Administrative Censoring



For PFS : Death Before Progression



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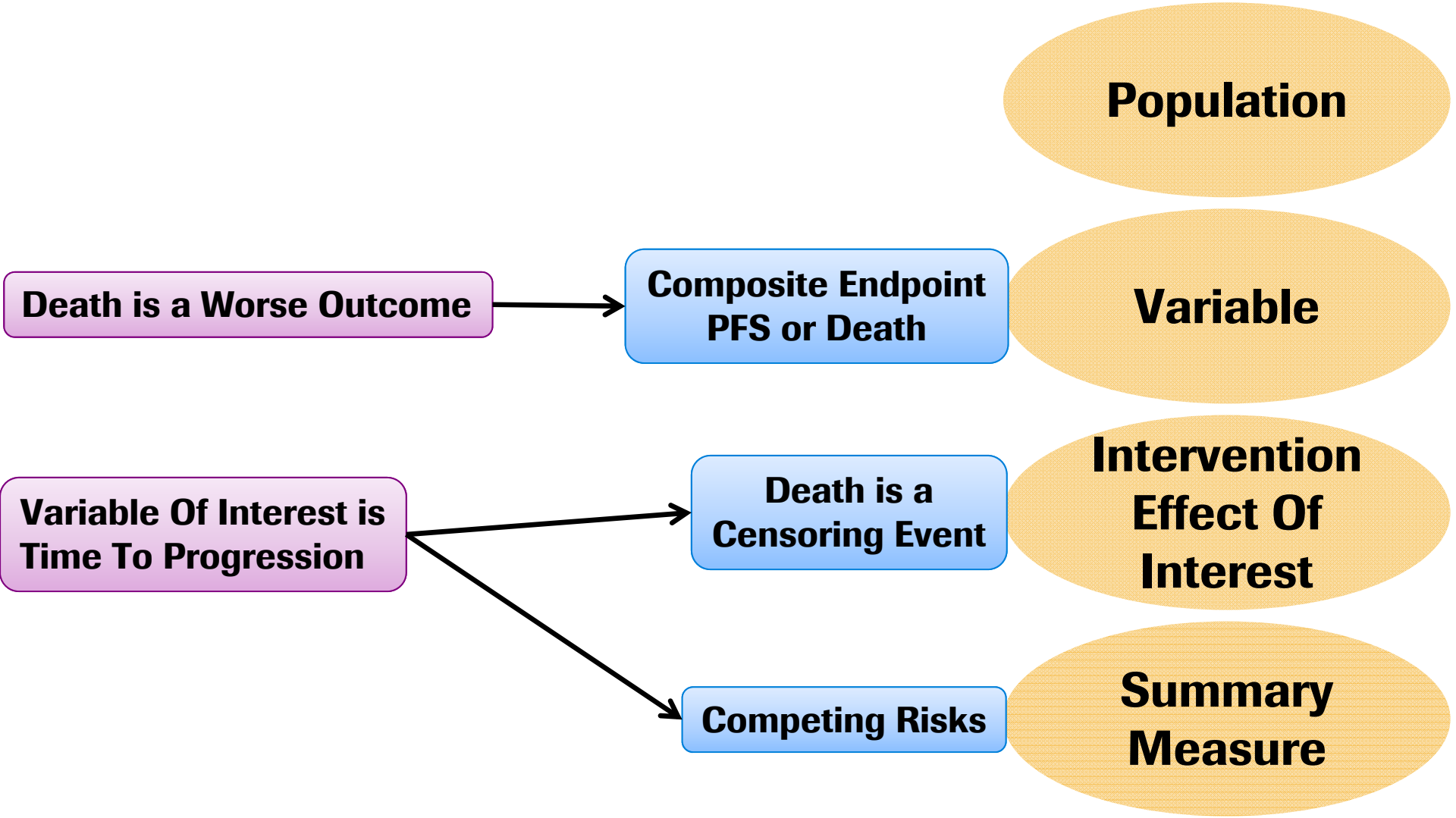
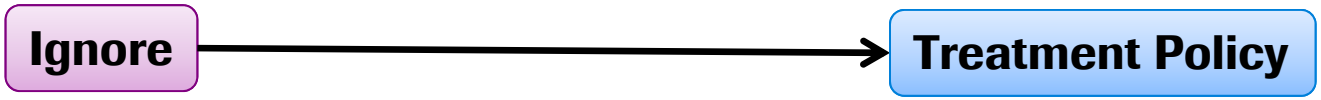


Treatment Switching



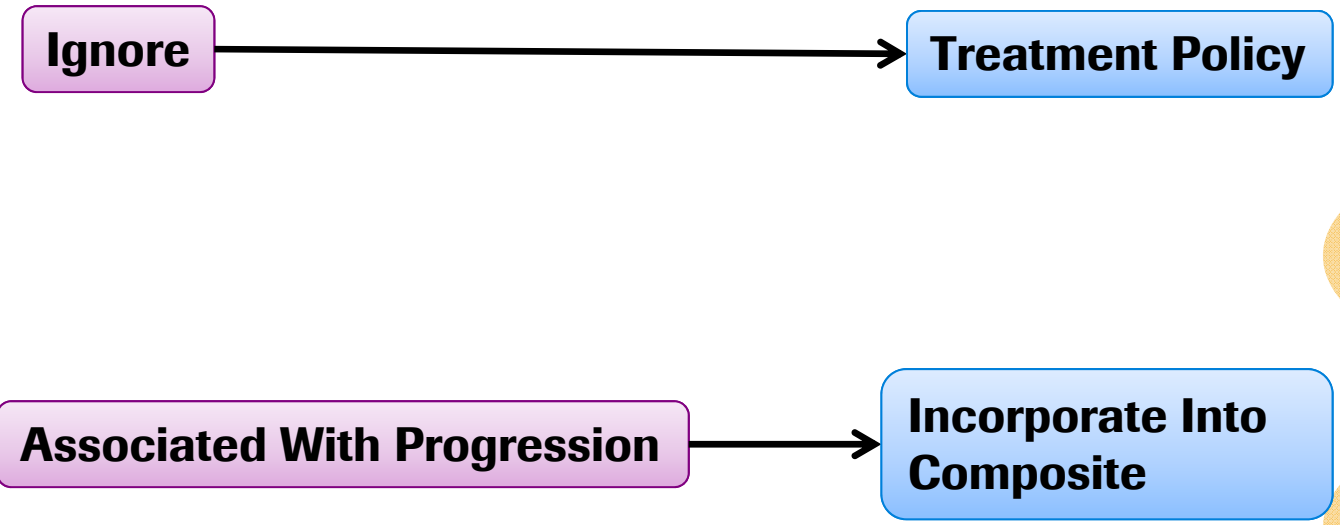
Population

Variable

Intervention Effect Of Interest

Summary Measure

Treatment Switching



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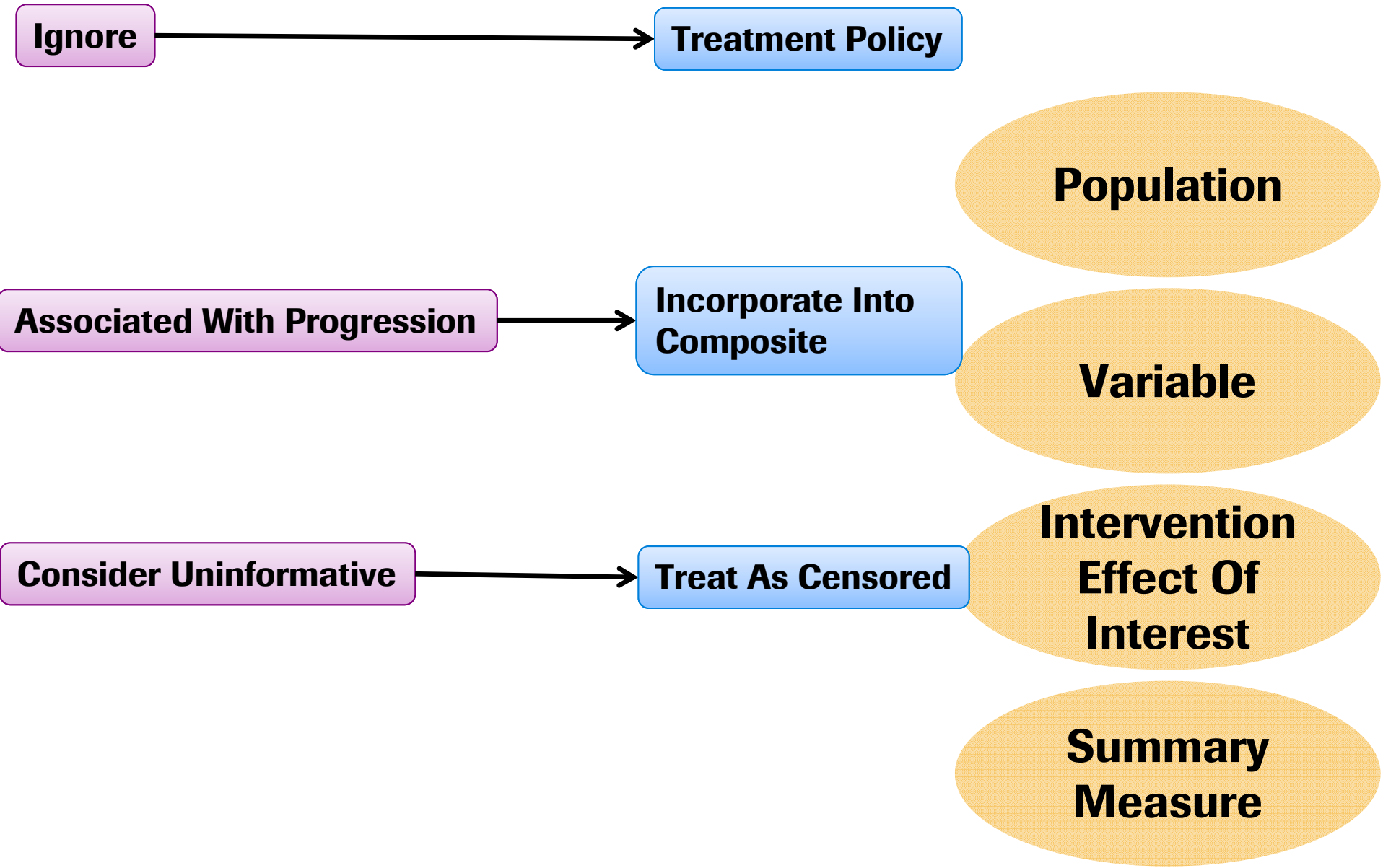

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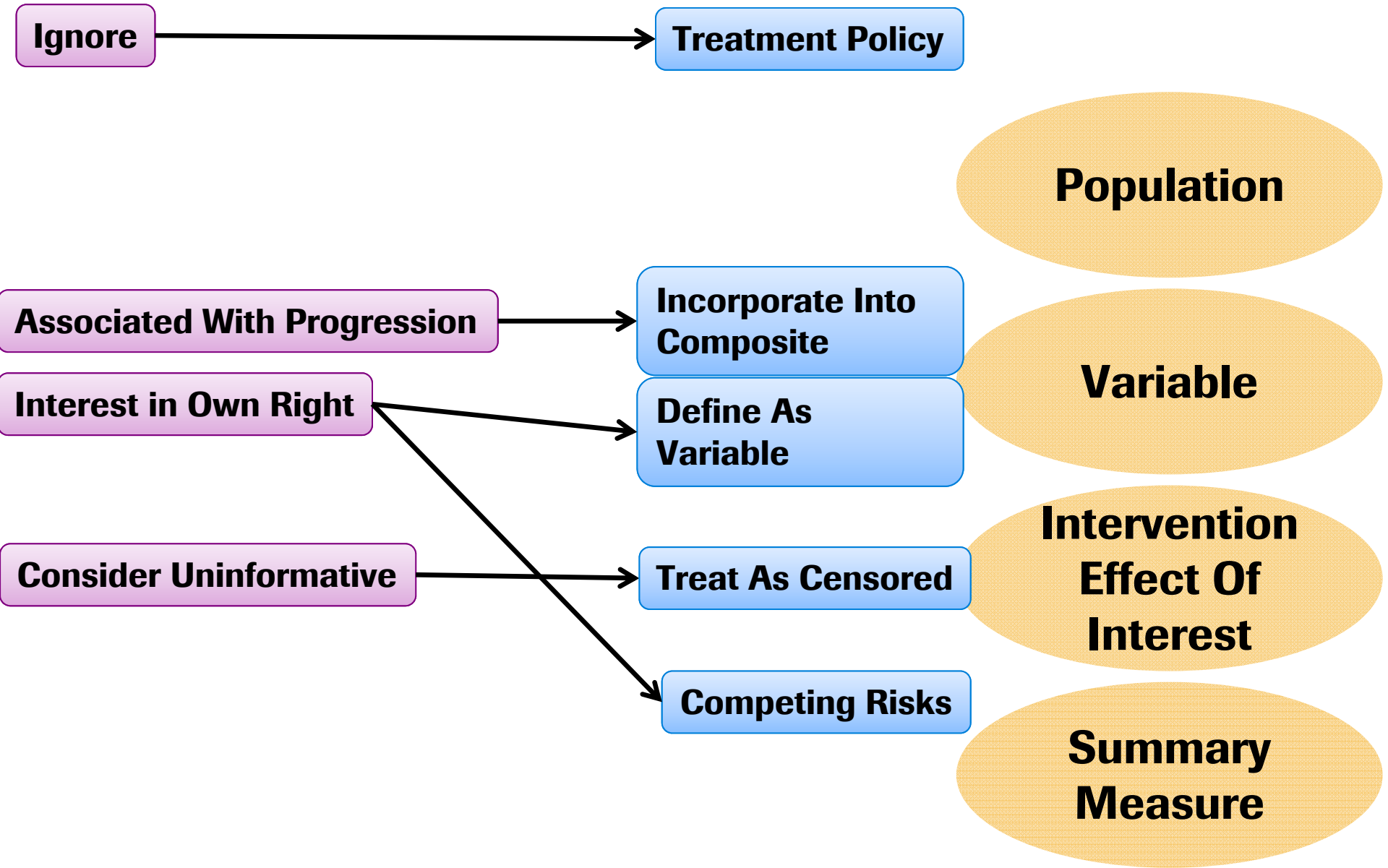

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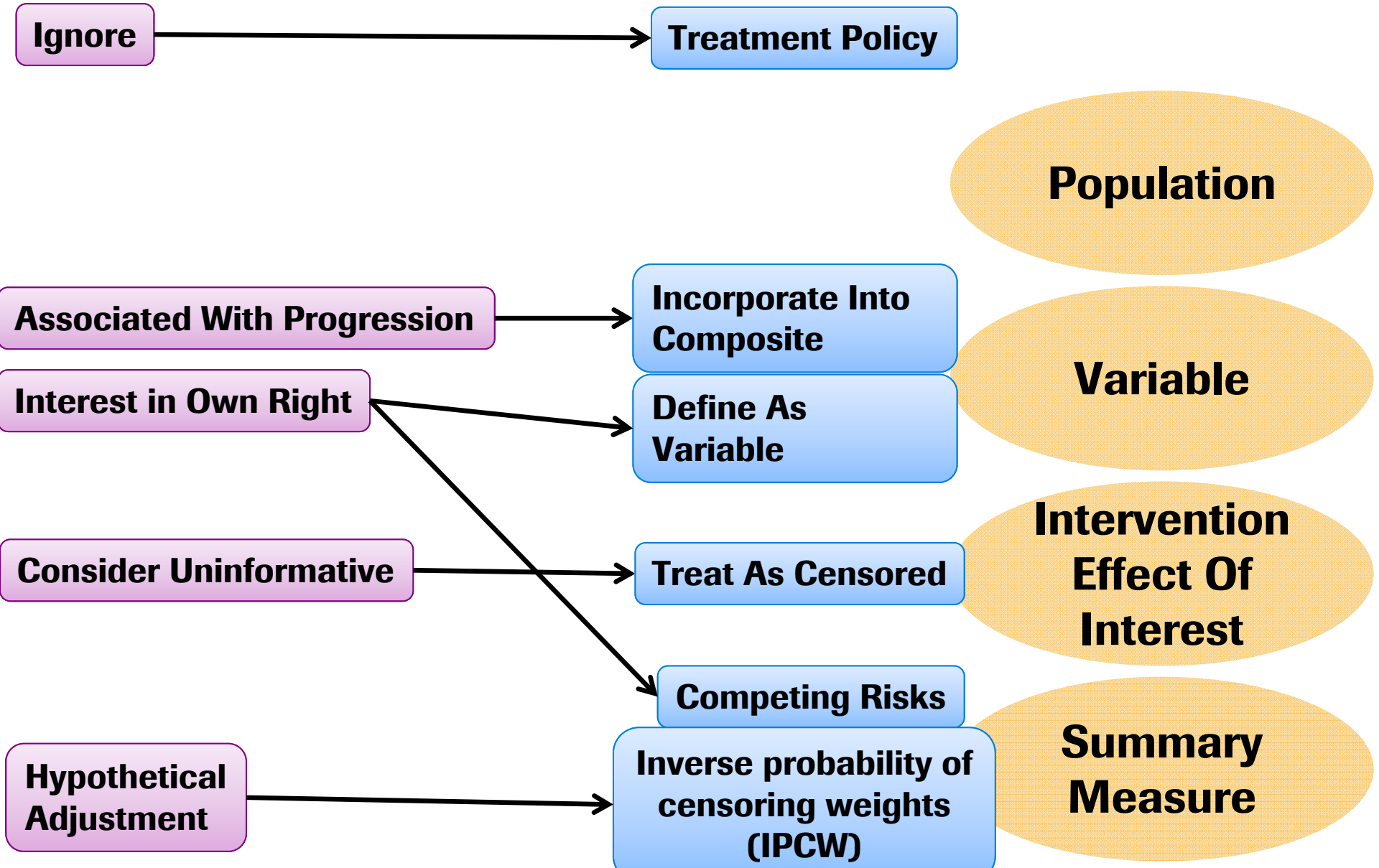
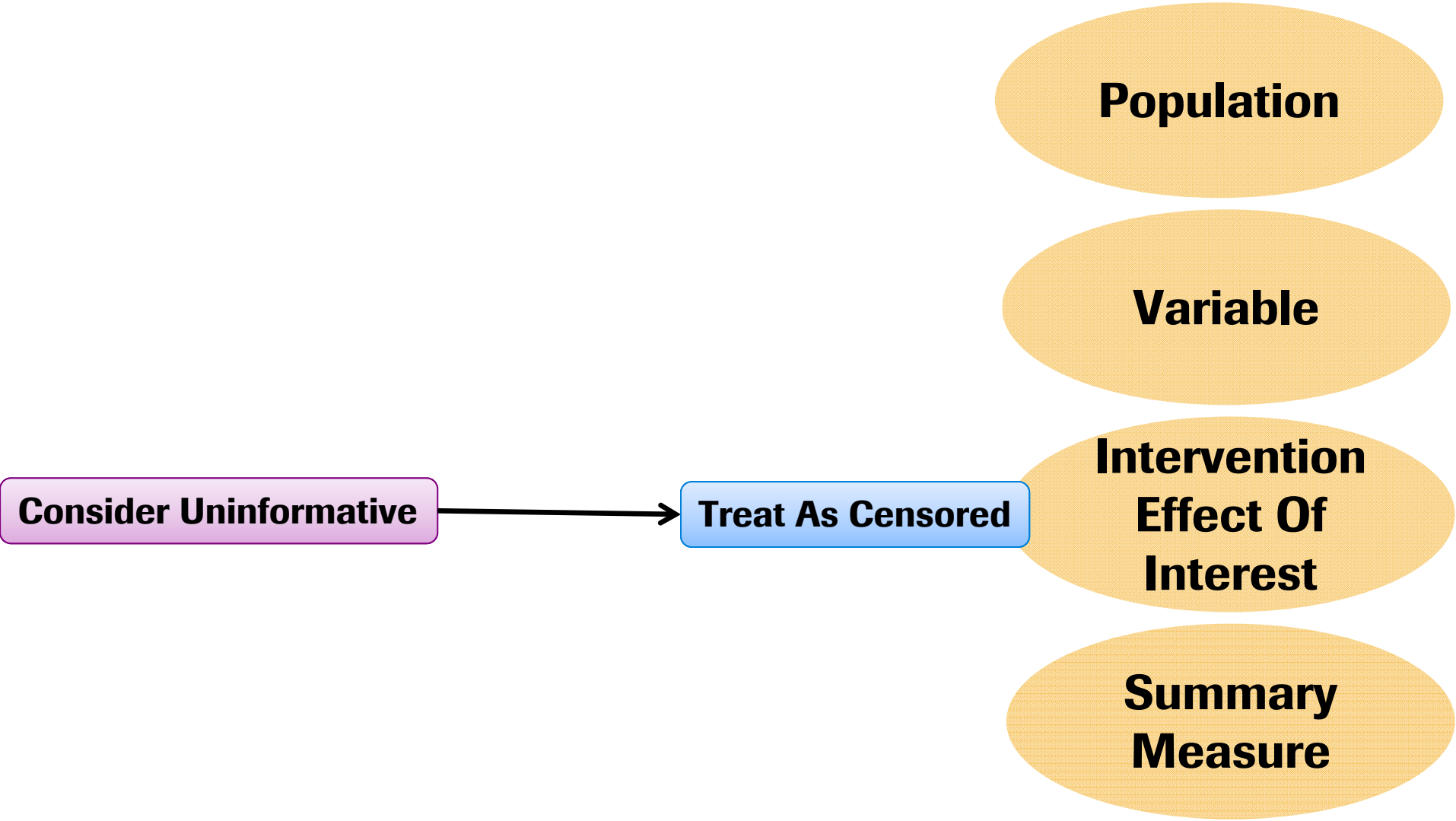


Early Withdrawals – Post-Randomisation , Pre-Treatment



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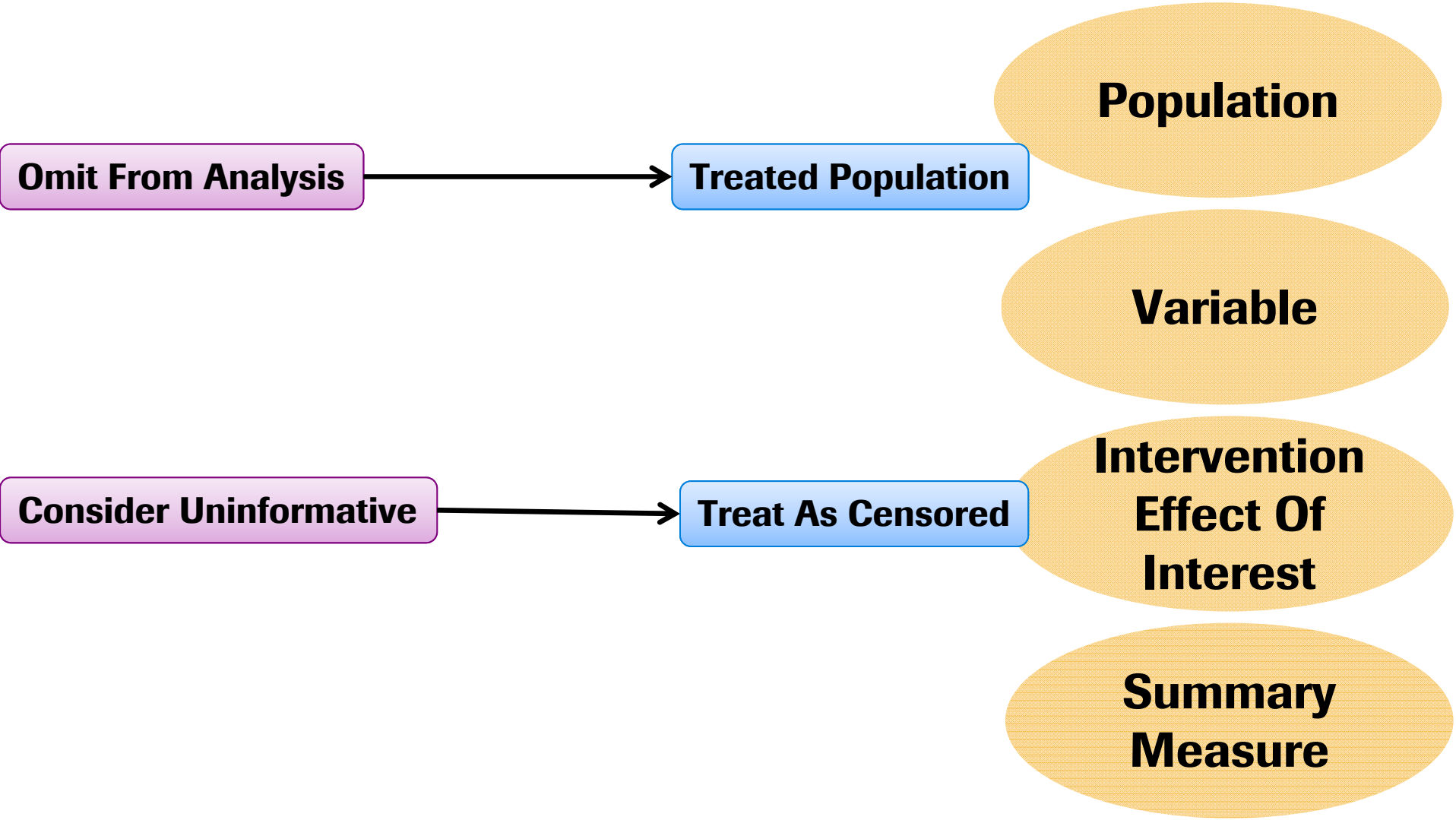

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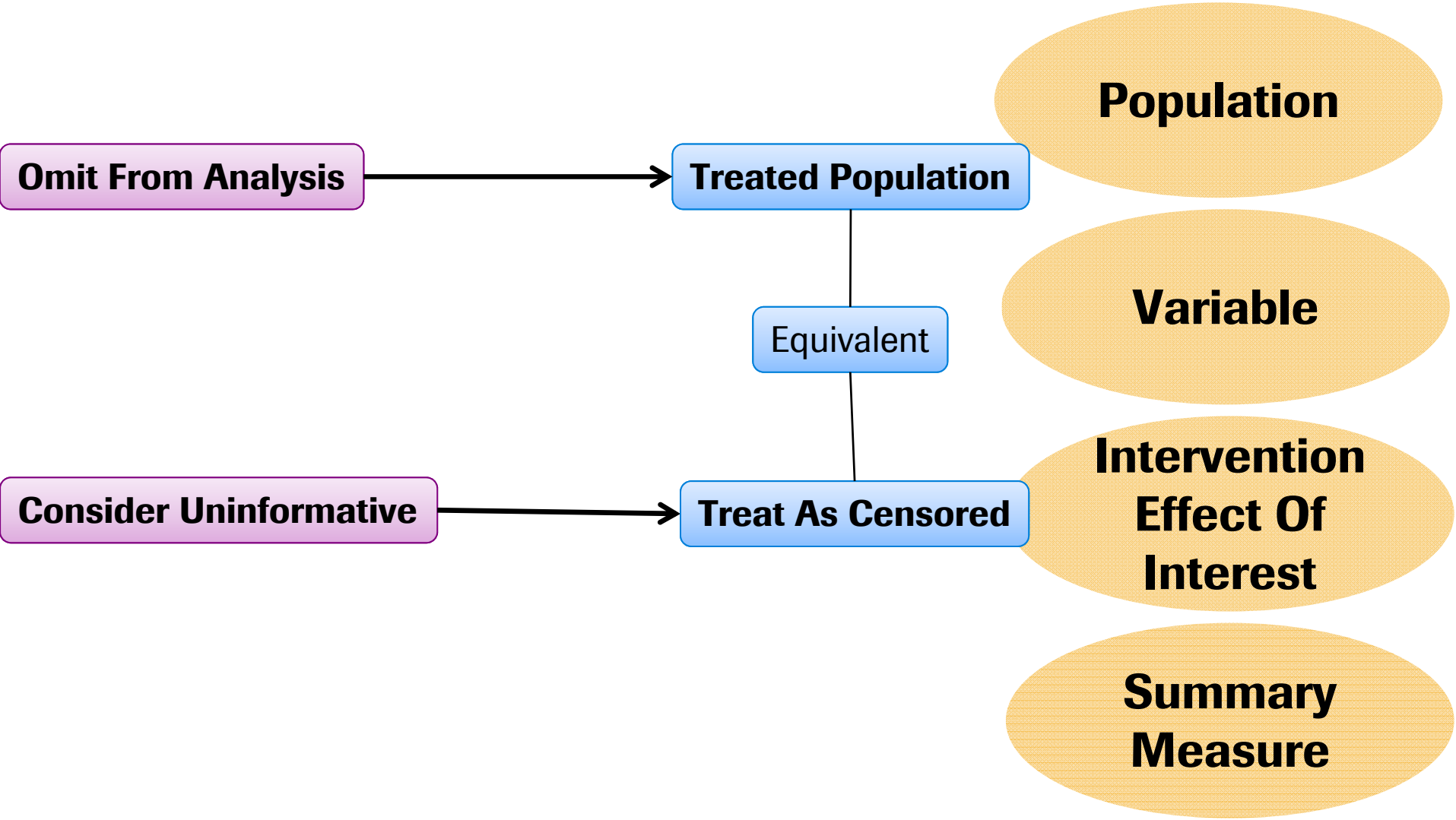

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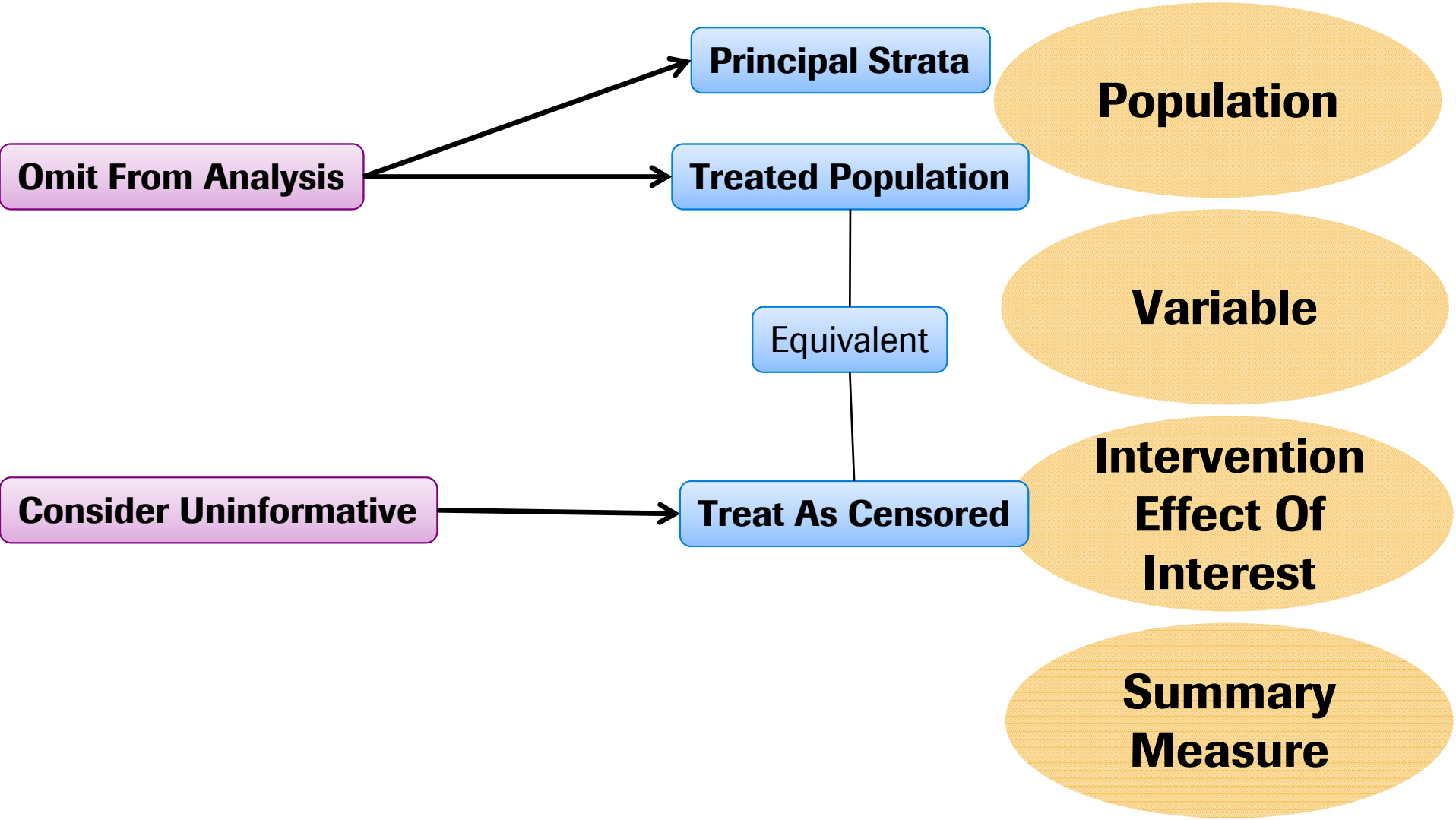
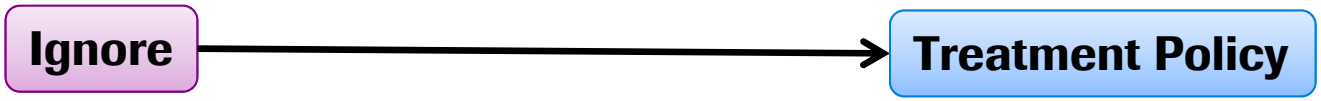


Treatment Withdrawals
Post- Starting Treatment



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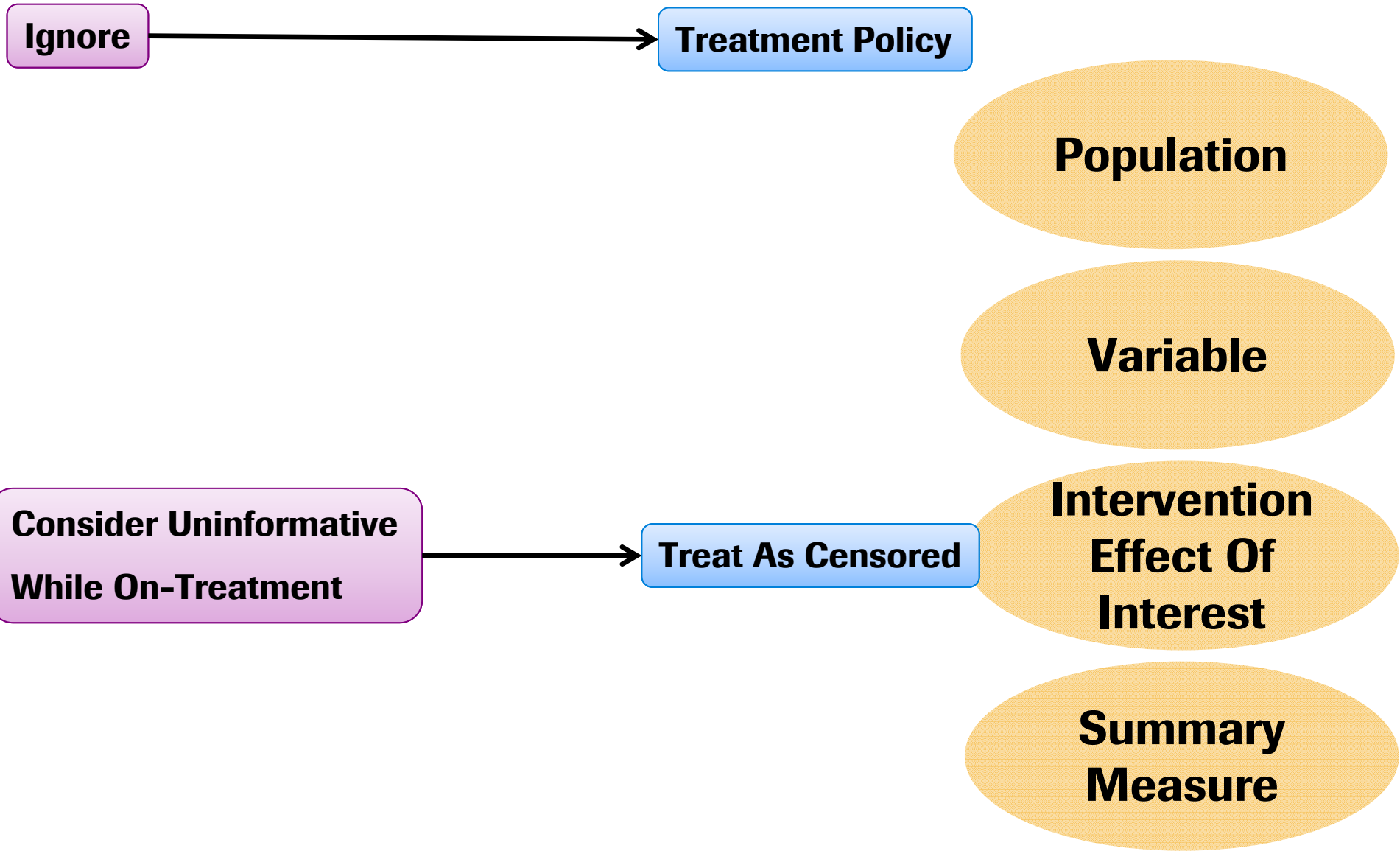
Treatment Withdrawals
Post- Starting Treatment



Treatment Withdrawals
Post- Starting Treatment

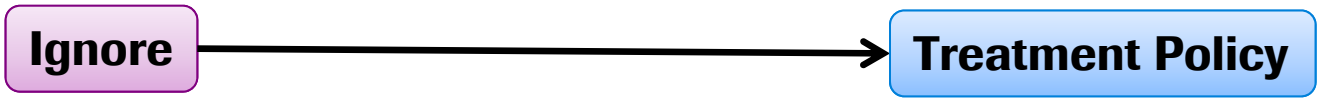
Ignore → Treatment Policy

Could potentially split out by reason for withdrawal (efficacy, safety, unrelated) and treat differently

Consider Uninformative While On-Treatment → Treat As Censored

- Population
- Variable
- Intervention Effect Of Interest
- Summary Measure

Dose Reductions



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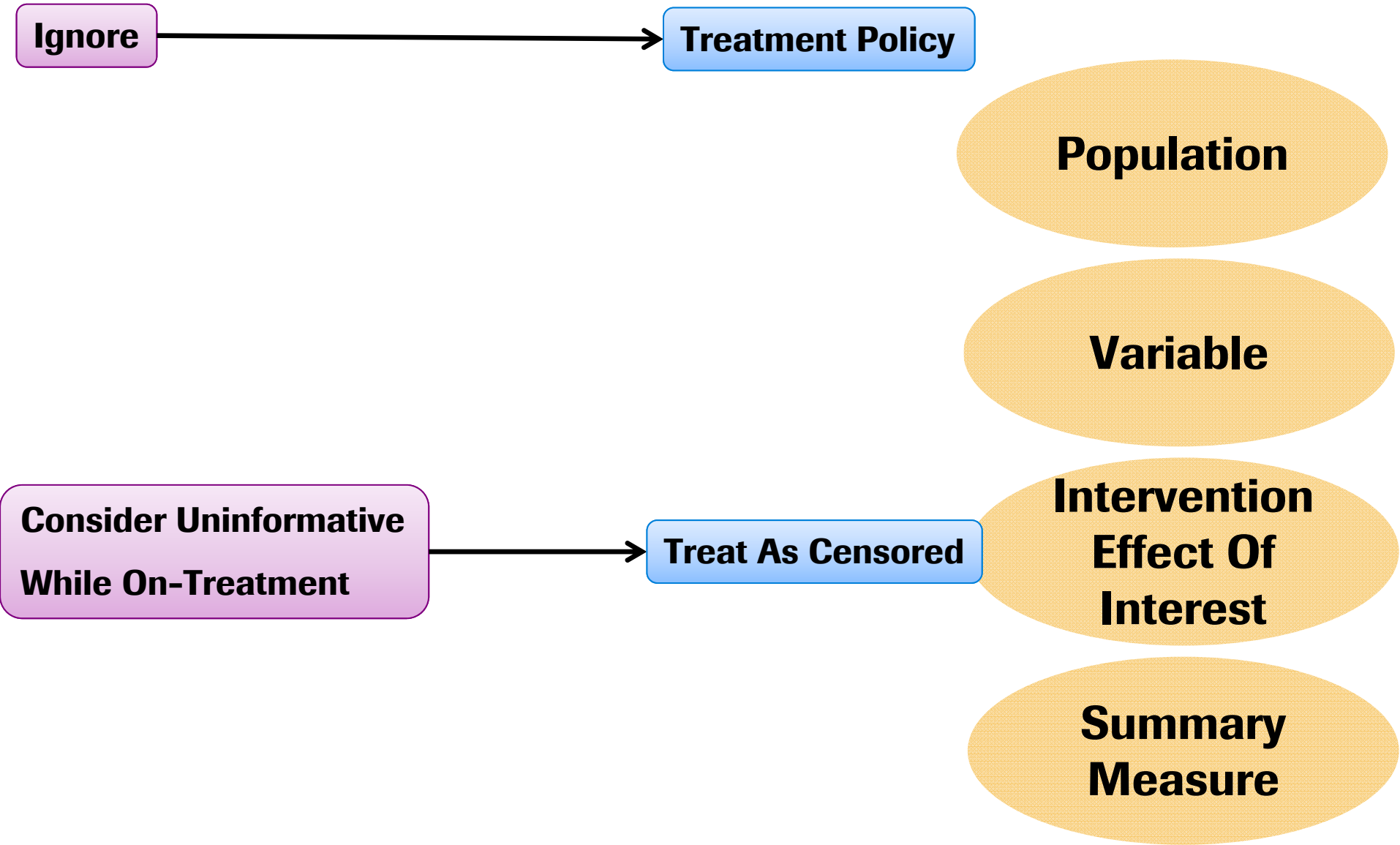
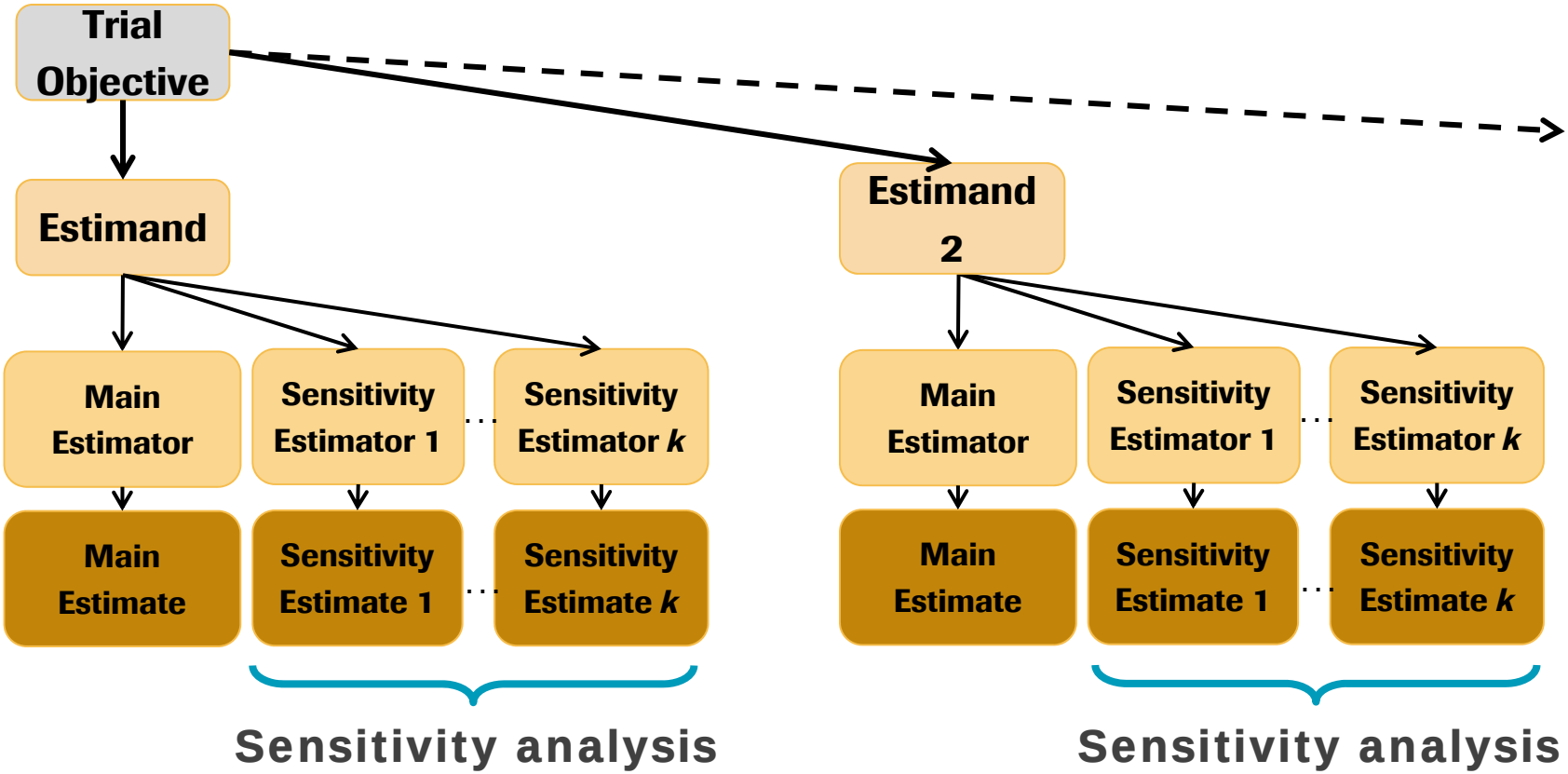


Sensitivity Analyses



Different estimands may require different numbers of sensitivity analyses

- **Importance of estimand**
- **Level of assumptions required in estimator**
  - **Treatment policy – fewer assumptions -> fewer sensitivity analyses**
  - **Hypothetical or Principal Strata -> modelling -> more sensitivity analyses**

Non-Hodgkin Lymphoma
DLBCL & FL : Two most common lymphomas, Often treated with the same agents

Follicular Lymphoma	Diffuse Large B-Cell Lymphoma
~20% of NHL diagnoses	~30% of NHL diagnoses
Indolent disease – cancer cells clump in lymph nodes	Aggressive disease – cancer cells spreading out
Late diagnosis	Diagnosis can be early
Many patients respond, but usually relapse	Highly responsive, good prognosis if respond, poor prognosis if relapse
Aim is to delay disease return	Aim is cure
New anti-lymphoma therapy (NALT) typically initiated after PD	Investigators tempted to initiate NALT if patient only achieves partial or stable response, even before PD

Non-Hodgkin Lymphoma
PFS: Event = PD/death, censored at last tumor assessment.

Estimand	PD	Death	No Response but no PD	NALT without PD
Fleming et al (2009): ”patients **should not be censored** at the time other treatments are initiated when analyzing the PFS endpoint”	E	E	-	-
Cheson et al (2007): ”…in studies in which failure to respond without progression is considered an indication for another therapy, such patients **should be censored** at that point for the progression analysis. ”	E	E	C (DLBCL) - (FL)	-
Event Free Survival	E	E	-	E
Time To Next Treatment	-	E	-	E

E=Included in composite endpoint, C=Censoring , - = Not considered

Are Estimands Necessary for Time-To-Event Endpoints?

Any Questions?

Doing now what patients need next

Abstract

Observed time-to-event endpoints typically contain many censored observations. As a consequence, many of the standard analysis approaches e.g. Kaplan-Meier and Proportional Hazards are specifically designed to address these partially missing data. This ability to cope with data being missing due to censoring has frequently led to the benefits of estimands for addressing other types of intercurrent events being overlooked.

In this presentation I will discuss how the estimand framework provides a vehicle for explicitly describing and addressing several of the challenges within time-to-event analyses such as treatment cross-over, informative censoring, lack of blinding and inconsistent definition of endpoints.