Lesson 6:

Risk Periods

- Initial treatment
- As treated
- Induction, latency, carry-over

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Implementation of New User Design

- To be consistent for all periods, define:
- Washout Period (WP) = minimum length of time that a patient must be drug-free prior to becoming eligible for the new user cohort
  - Note: usually includes all comparators!
- Grace Period (GP) = maximum length of time that a user can go without the drug before being considered discontinued from drug use (e.g., 15, 30, 90, 180 days)
- Days Supply (DS) = imputed number of days supply to use as Days Supply when true value is unknown (e.g., 30 days)

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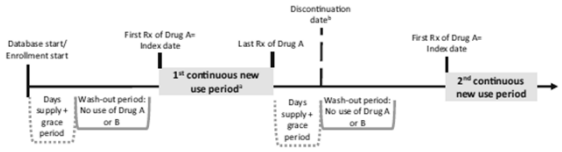
Implementation of New User Design



Lund JL, Current Epidemiology Reports, 2015

Additional study timeline considerations:
- Induction/lag periods
- Latent/detection periods

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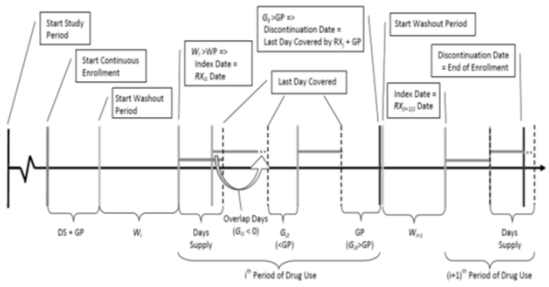
Implementation of New User Design



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Conclusions Active Comparator New User Study Design

- Conditioning on indication has major impact on potential for confounding by indication and frailty
- Can in practice only be achieved with active comparator new user (ACNU) design
  - no non-experimental "placebo"?
- Carefully assess potential for remaining confounding by indication (clinical input)
- Standard design in non-experimental PE and CER (need to argue deviations!)

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Treatment Changes During Follow-Up

- Stopping
  - No refill after defined period of time
  - Days supply
  - Grace period (allow for some non-adherence)
- Switching
  - Prescription of other treatment arm
  - No refill of original treatment within DS+GP
- Augmenting
  - Prescription of other treatment arm
  - Refill of original treatment within DS+GP

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Time-Varying Confounding

- Easy if measured and not affected by prior treatment (e.g., age)
- In PE: both conditions often not met
  - Unmeasured (badly measured)
  - Affected by prior treatment
  - E.g., Asthma severity
- If measured and affected (e.g., CD4-count, blood pressure, lipids): MSM, G-methods
- Often better: new user design & censor at time of treatment changes
  - Stopping, switching, augmenting
  - Cave: selection bias

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Selection Bias

- Censoring for treatment changes can introduce selection bias
- Solution:
  - Initial treatment (RCT: ITT)
    - Works well for short term effects
    - Long term effects?
  - If measurable: MSM, G-methods
    - Prediction of adherence difficult/impossible?

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Initial Treatment (IT)

- Avoids selection bias due to treatment changes
- RCT equivalent: Intent-to-treat (ITT)
  - Note: not the same - think about differences!
- Downside: increasing exposure misclassification over time since initiation
- Tends to bias results towards the null
  - Possible bias over the null!
- Note: still need to censor for
  - Loss of eligibility
  - Death
  - Important to avoid "immortal" time

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As Treated (AT)

- RCT: "per protocol"
  - Censor at stopping/switching/augmenting
  - Note: not the same - think about differences!
- Sensitivity analyses
  - Add latency period ("carry-over") after stopping/switching/augmenting
  - E.g., 3, 6, 12 months
  - Extreme: initial treatment
  - Discuss pattern based on potential for bias
  - Count both person-time and events!

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"Final Words" Time-Varying Confounding & Selection Bias

- Cave time varying treatment models
  - Time-varying confounding/selection bias by
    - Disease progression (indication), (lack of) effectiveness, side effects, frailty, healthy adherer
  - Impossible/hard to measure, affected by prior Rx
- Time-varying Cox model
  - No clear timeline (T_0?); often invalid
- MSM sensitive to violation of no unmeasured confounding assumption (weights multiply!)
- NU design with IT avoids pitfalls: principled!
- As treated (AT) often necessary

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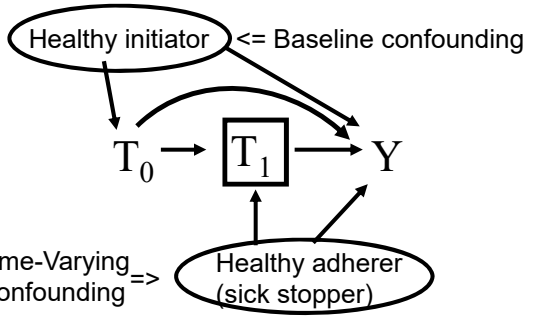
Remember: DAG



When conditioning on T_1 by censoring if T_1=0 => selection bias

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Induction, Latency, Carry-Over

- Induction period (Rothman 81):
  - Period of time form causation until disease initiation in reference to component cause
- Latent period (Rothman 81):
  - Interval after disease initiation until the disease first is detected
- Carry-over effect:
  - Effect that "carries over" from one experimental condition to another (1st three hits on google)

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Latent Period

- Disease onset -> symptoms -> medical attention -> diagnosis
- Practically, of course, the precise point at which disease is initiated cannot be determined, and consequently any attempt to measure induction period will include the latent period as well (Rothman 81)
- Often implicitly included in induction period!
- Added after stopping/switching (technically: after stopping plus carry-over)

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Carry-Over Effect

- Pharmacokinetics (clearance, half-life, volume of distribution)
- Pharmacodynamics
- Often orders of magnitude shorter than latent period
- In PE sometimes used to define latent period

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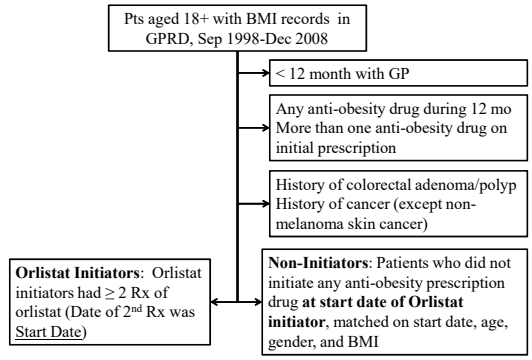
Example: Orlistat and CRC Study



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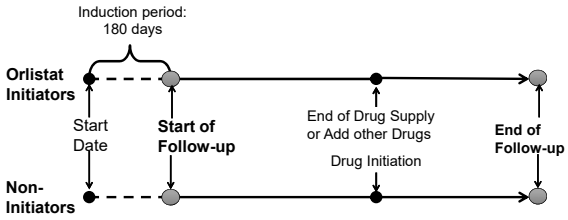
Initial Treatment Design



Follow-up ends at a time of CRC, any other cancer, death, or migration out of GP

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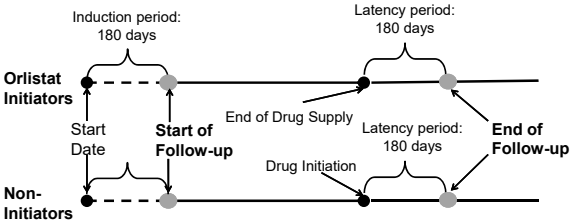
As-Treated Design



Follow-up ends latest 180 days after drug discontinuation/initiation

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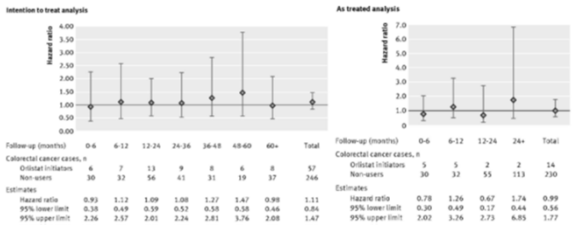
HR Stratified by Time Since Initiation



Hong et al., BMJ 2013;347:f5039

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Sensitivity Analyses

Table 4| **Sensitivity analysis for induction and latency period in as treated analysis**

Induction period (days)	Latency period (days)	Cohort	No of colorectal cancers	No of observations	Follow-up (years)—median (interquartile range)	Weighted hazard ratio (95% CI)
0	180	Orlistat initiators	15	33 625	1.21 (1.06-1.60)	0.77 (0.44 to 1.34)
		Non-initiators	256	160 347	2.61 (1.25-4.75)	1.00
90	180	Orlistat initiators	14	32 501	0.97 (0.82-1.37)	0.85 (0.47 to 1.52)
		Non-initiators	244	153 659	2.49 (1.16-4.64)	1.00
180	180	Orlistat initiators	14	31 055	0.75 (0.57-1.16)	0.99 (0.56 to 1.77)
		Non-initiators	230	146 133	2.40 (1.08-4.60)	1.00
365	180	Orlistat initiators	9	27 234	0.32 (0.13-0.73)	1.12 (0.56 to 2.24)
		Non-initiators	199	128 276	2.32 (1.05-4.48)	1.00
180	0	Orlistat initiators	7	29 719	0.33 (0.14-0.76)	0.89 (0.40 to 2.01)
		Non-initiators	229	141 562	2.44 (1.12-4.66)	1.00
180	90	Orlistat initiators	11	30 387	0.55 (0.32-0.96)	0.99 (0.52 to 1.90)
		Non-initiators	230	143 532	2.42 (1.11-4.64)	1.00
180	180	Orlistat initiators	14	31 055	0.75 (0.57-1.16)	0.99 (0.56 to 1.77)
		Non-initiators	230	146 133	2.40 (1.08-4.60)	1.00
180	365	Orlistat initiators	18	31 055	1.21 (1.08-1.60)	0.86 (0.52 to 1.41)
		Non-initiators	231	146 133	2.47 (1.17-4.66)	1.00
180	730	Orlistat initiators	32	31 055	2.08 (1.43-2.45)	1.03 (0.70 to 1.50)
		Non-initiators	236	146 133	2.62 (1.34-4.77)	1.00

Hong et al., BMJ 2013;347:f5039

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