Summer Institute in Statistics for Clinical Research

Obtaining insights

to recognize and effectively address scientifically challenging issues in

- Design
- Conduct
- Analysis/Reporting

of clinical trials

Summer Institute in Statistics for Clinical Research

Addressing Missing Data in Clinical Trials

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Rivaroxiban in ACS
FDA CRDAC '12; '14

NRC, 2010. "*The Prevention and Treatment of Missing Data in Clinical Trials*". Washington DC. National Academies Press

Fleming TR "Addressing Missing Data in Clinical Trials". *Annals of Internal Medicine* 2011; 154: 113-117

Goal of Clinical Research

To achieve a timely and *reliable* evaluation of an intervention's benefit-to-risk profile

Solution:

The design and conduct of the trial should minimize:

- Variability
- Bias

E.g.: 6MWD in PAH

How do we control bias?

Randomization

Adherence to Interventions

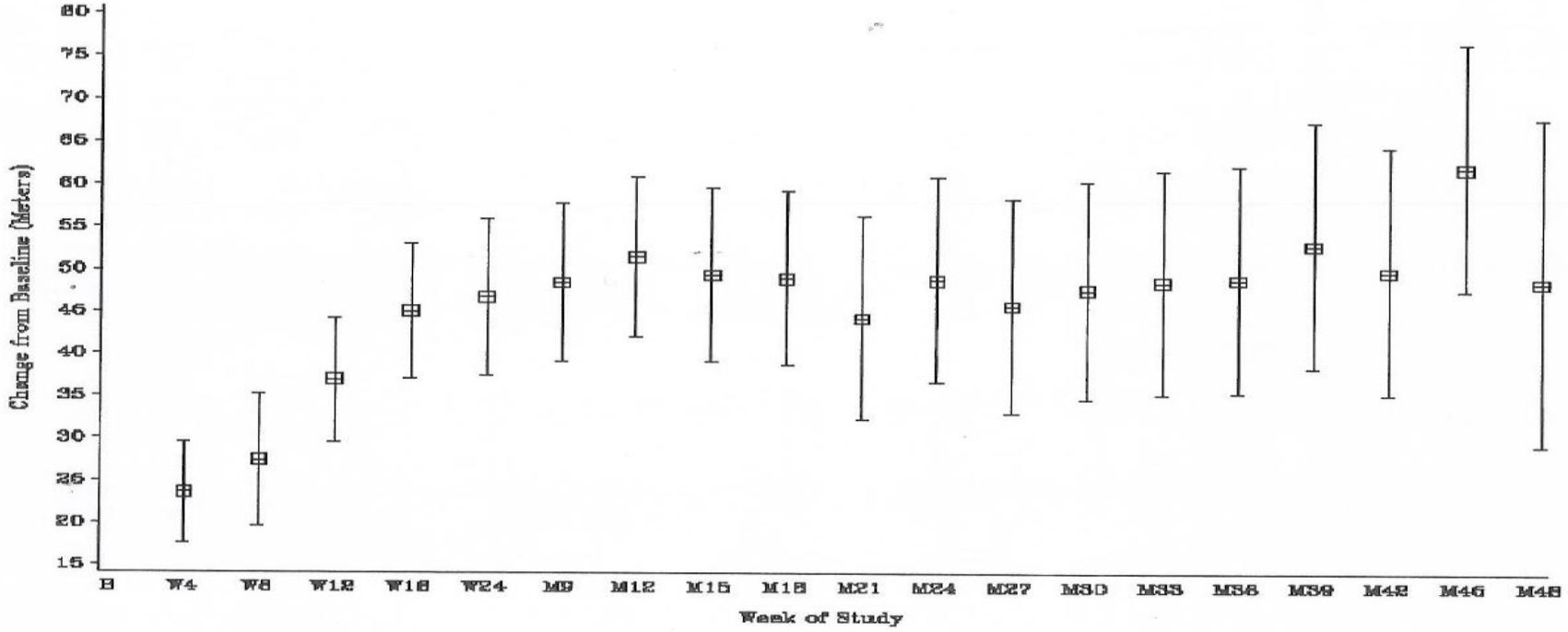
Intention to Treat Analyses

High Levels of Retention/Follow-up

Approaches to Address Missing Data

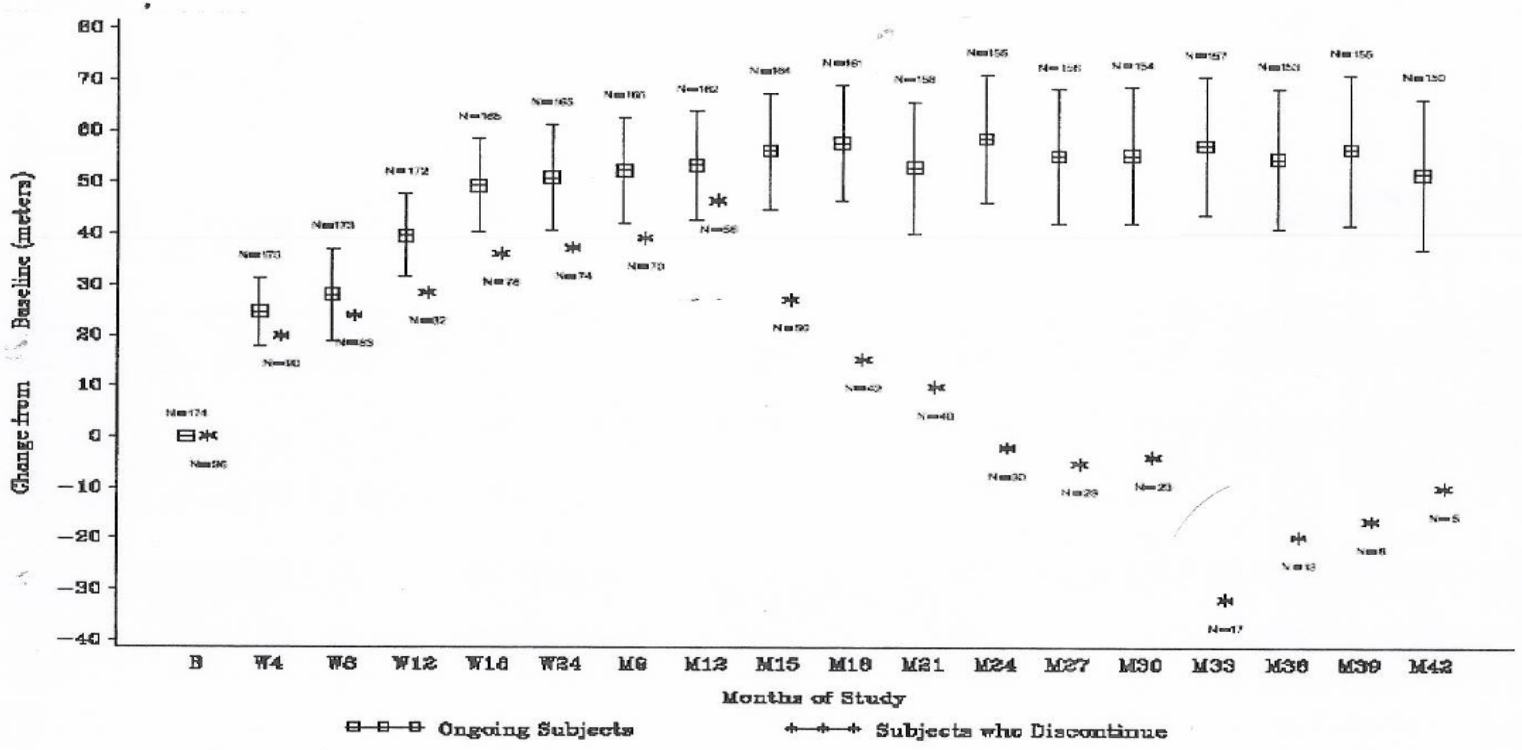
- Overly simplistic approaches to data imputation:
  - ✓ Last Observation Carried Forward (LOCF) E.g. ARMD
    ...Is the *present* an unbiased estimate of the *future*?
    Annals of Internal Medicine: LOCF not acceptable
  - ✓ Complete Case Analysis
    …Are incomplete data "*Missing Completely at Random*"?
  - ✓ Worst Case Analysis E.g. Prevention of rare outcomes
    …Worst Case for patient, but not for R_x effect estimates
    …Would the patient have been a failure if assessed?

Missing Data Inducing Dependent Censoring Illustration: Complete Case Analysis

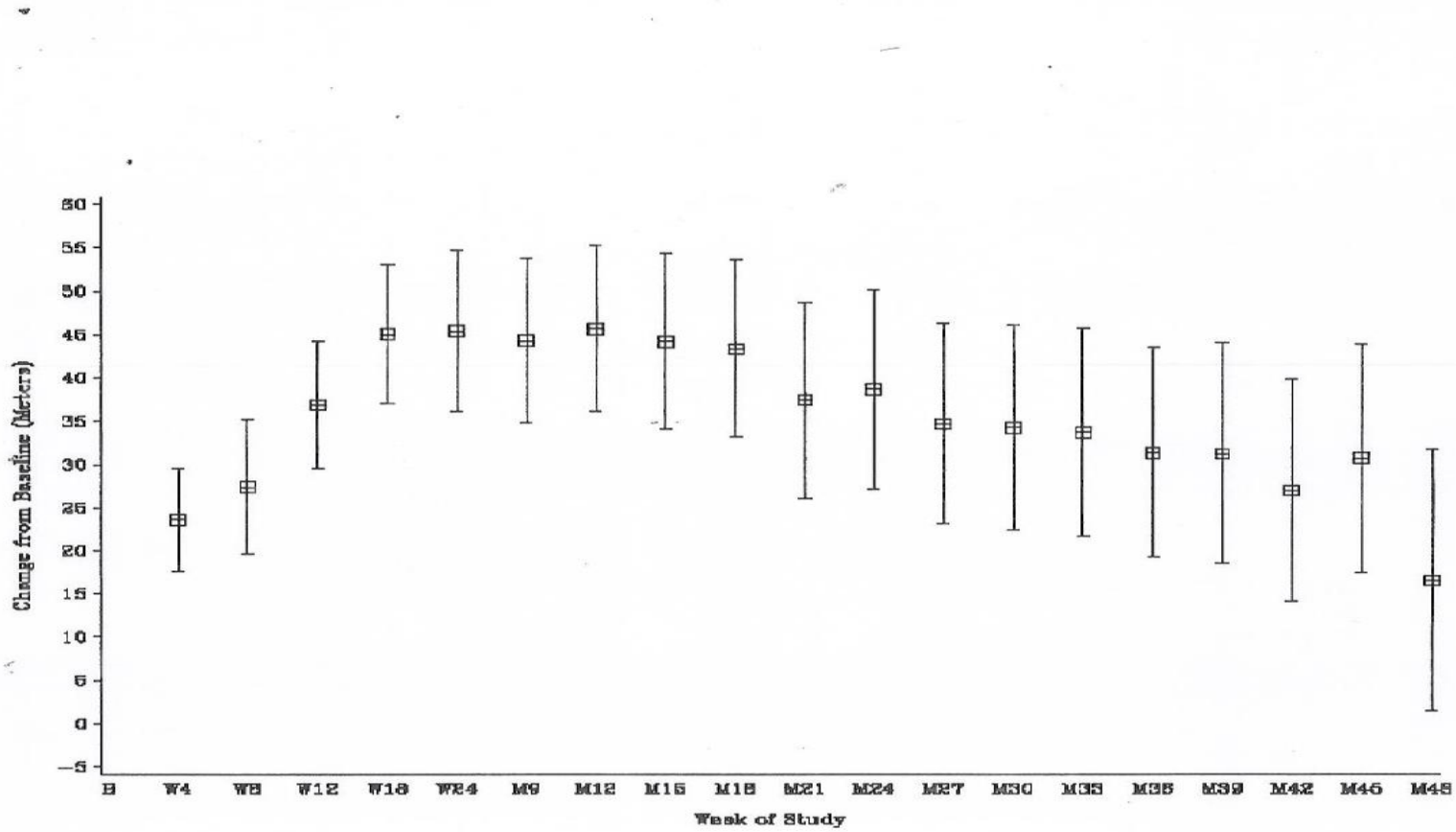


Missing Data Inducing Dependent Censoring

Distinguishing Ongoing from Discontinuing Subjects



Missing Data Inducing Dependent Censoring Illustration: Using LOCF for Missing Data



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    …Would the patient have been a failure if assessed?
- The preferred approach to handling missing data:
  …**Prevent it** by obtaining outcome evaluations in all surviving patients who haven't withdrawn consent

Factors commonly contributing to Unacceptable levels of Missing Data

- ✓ Lack of proper distinction in protocols between reasons for non-adherence versus non-retention… **"Dropouts"**
  i.e. reasons for "off study treatment" vs. "off study"
  "Off study" only for: Death or Withdrawal of Consent
- ✓ Misuse of the term "Withdrawal of Consent" (WC)
  Often 5-10% when it should be 1% (5% in anti-psychotic)

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E.g.: Rivaroxaban (Anticoagulant) in Acute Coronary Syndrome
FDA Cardio-Renal Drugs Advisory Committee 5/23/2012; 1/16/2014

Regimen	N	CVD/S/MI	HR	(95% C.I.)
2.5 mg BID	5174	315	**0.84**	(0.72, **0.97**)
5.0 mg BID	5176	319	**0.86**	(0.74, **1.00**)
Placebo	5176	378		

12% missing data; **8%** due to "Withdrawal of Consent"

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- ✓ Misuse of the term "Withdrawal of Consent" (WC)
  Often 5-10% when it should be 1% (5% in anti-psychotic)
- ✓ Lack of clarity in the Informed Consent process regarding impact of incomplete capture of outcomes on trial integrity and credibility

Participants should be informed they can WC at any time, but should also be informed that missing data diminishes the scientific value of the all patients' altruistic contributions

Factors commonly contributing to Unacceptable levels of Missing Data

✓ Lack of clarity that, for ITT analyses, all patients should be followed until death or trial completion, even if off study treatment or initiation of other treatment

ITT analyses:

- Preserve the integrity of randomization
- Due to their unconditional nature, address the questions of most important scientific relevance
- Properly evaluate the experimental intervention in the context of a regimen

	Control Regimen		Microbicide	
	PYs f.u.	2 YR Rate	PYs f.u.	2 YR Rate
"Adherent" 60%				
Followed	50%	20%	50%	8%
LFU	10%	20%	- -	-
Tox ⇒ Non-compl	- -	-	10%	80%
"Non-adherent" 40%				
Followed	- -	-	- -	-
LFU	40%	35%	40%	35%

AT 2 YEARS

Actual HIV Rate	26%	26%

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ITT Analyses: Preserving Integrity of Randomization

"*To preserve the integrity of randomization, all patients should be followed until the complete capture of trial outcomes, even after patients have discontinued randomized treatment or initiated other interventions. Achieving such follow-up enables the conduct of a proper "as-randomized" analysis in which the study outcome is assessed in all patients. This analysis evaluates an intervention as part of an experimental regimen that also includes effects of ancillary care and rescue therapy that might be provided to patients and addresses the questions of greatest relevance because of its unconditional nature.*" *(Fleming Ann of Int Med 2011;154: 113-117)*

Typically, the occurrence of an intercurrent event is part of the treatment effect; that doesn't invalidate the ITT analysis or its clinical relevance. One might consider the effect of the experimental intervention on the occurrence of the intercurrent event as a supportive analysis or supportive endpoint.

Factors commonly contributing to Unacceptable levels of Missing Data

- ✓ Protocols indicating that sample size adjustments have been made to address expected levels of missing data, projected to be high, often in the range of 10-50%

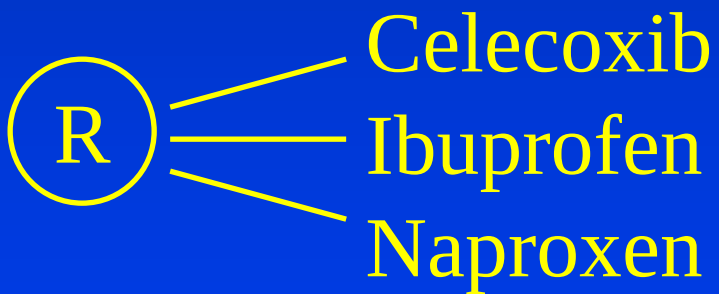
There is a lack of clarification that such adjustments only address the variability, and not the bias, of missing data, resulting in obtaining "more precise *biased* estimates"

- ✓ Lack of clarity in protocols about performance standards for quality of trial conduct, including targeted levels of data capture

- ✓ Lack of clarity in protocols regarding procedures during enrollment and follow-up to achieve high levels of retention

The PRECISION Trial: *Ruling out* Excess Rates of CV Death / Stroke / MI

Pain Medications in Patients with Osteoarthritis & Rheumatoid Arthritis With or at Hi Risk for CV Disease



Performance Standards in Non-inferiority Safety Trials

- **Enrollment Rate**
  - ✓ need timely result
- **Target Population / Ineligibility Rate / Event Rate**
  - ✓ need to address settings where excess risk is most plausible
  - ✓ need sufficiently high risk to achieve targeted number of events
- **Adherence**
  - ✓ must at least match adherence in prior trials with safety signal
  - ✓ include frequency/timing of withdrawal from rand. treatment
- **Cross-ins**
  - ✓ minimize by: careful screening; educating caregivers & patients

…*Very challenging in a post-marketing setting*…

- **Retention**
  - ✓ critical to maintaining integrity of randomization

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- ✓ **Lack of clarity in protocols regarding procedures during enrollment and follow-up to achieve high levels of retention**

Prevention of HIV Vertical Transmission

- Mothers/Infants in HIVNET 012 Trial

Challenging Issue: Given that mother/infant pairs, without home addresses, would be enrolled and treated at Old Mulago Hospital in Kampala, Uganda, how could the targeted 95% levels of retention be achieved over 18 months post delivery?

Retention of Participants in HIVNET 012
The Role of "Health Visitors"

- ✓ A Health Visitor was public health nurse/midwife, trained as a health social worker, community health educator and home visitor for maternal/child health, and was responsible for follow-up of study participants
- ✓ Each study participant was assigned a Health Visitor, allocated by geographical area
- ✓ Health Visitors retained participants by creating a rapport, at first with the participants and then with their families
- ✓ Locator information was obtained from the participants and a map drawn in order to help the Health Visitor know where to find the participant for effective follow-up

Retention of Participants in HIVNET 012
The Role of "Health Visitors"

- ✓ Health Visitors assured the participants of their confidentiality, allowing them to ask questions about anything related to the study
- ✓ Health Visitors provided ongoing health education about primary health care components such as nutrition, home sanitation, family planning, immunizations
- ✓ Health Visitors observed customer care principles, making participants comfortable and thanking them when they came for scheduled visits to the clinic, and demonstrated caring attitudes towards the sick

Retention of Participants in HIVNET 012
The Role of "Health Visitors"

- ✓ Health Visitors made regular home visits to keep close contact, strengthen relationships, and provide reminders about scheduled visits
- ✓ Health Visitors recorded and reported daily activities in log books and report forms
- ✓ Health Visitors held monthly meetings to evaluate their activities and solve problems, and attended regular meetings with the trial's Principal Investigators and Study Coordinators to share updates on each participant

Acknowledgments: Professor Mmiro, Laura Guay, Joanita Nankya

Prevention of HIV Vertical Transmission

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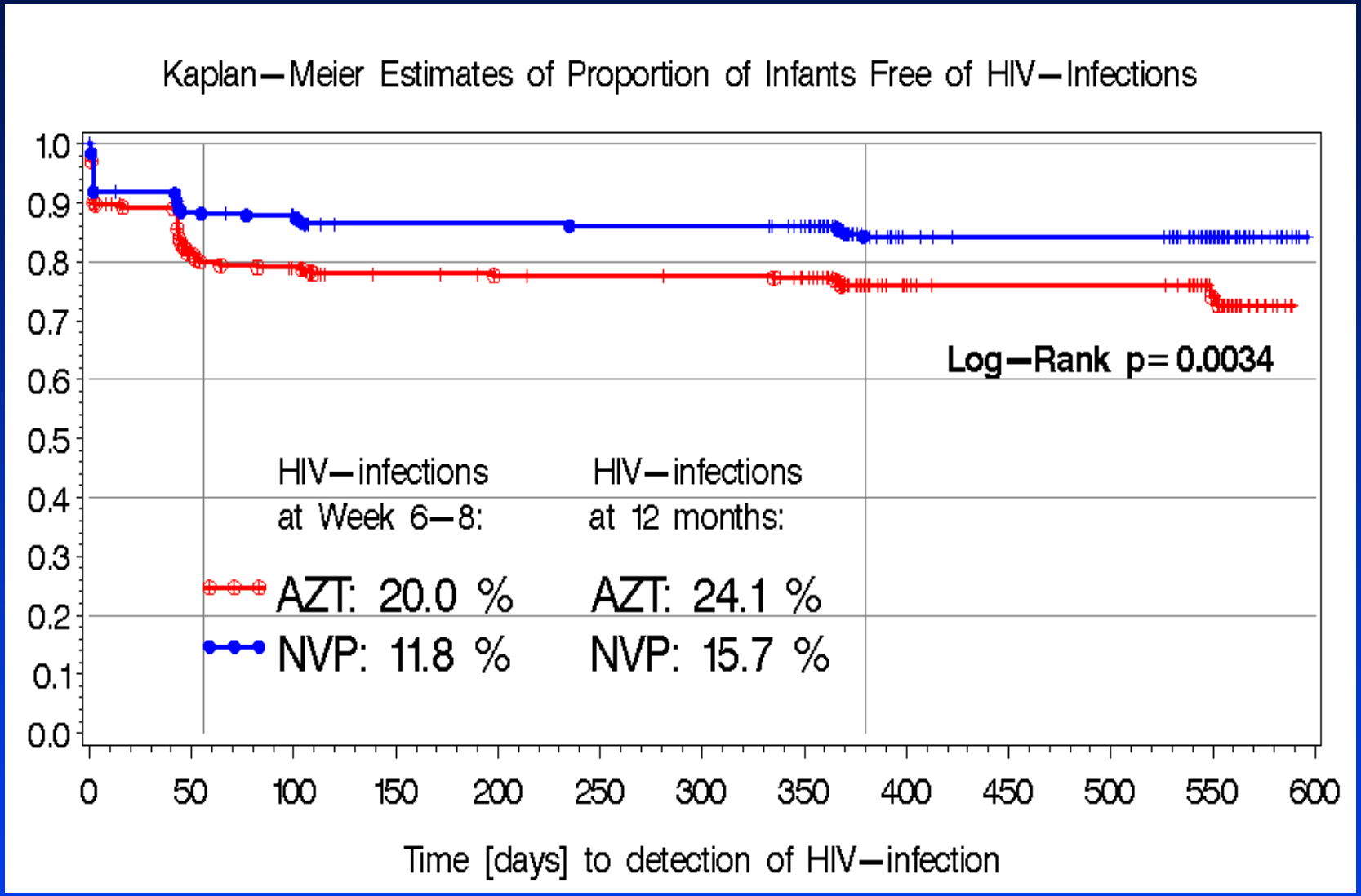
Challenging Issue: Given that mother/infant pairs, without home addresses, would be enrolled and treated at Old Mulago Hospital in Kampala, Uganda, how could levels of retention targeted for at least 95% be achieved over 18 months post delivery?

HIV TRANSMISSION THROUGH 18 MONTHS



HIVNET 012
Infection information available for analysis

	AZT	Nevirapine	Total
Enrolled	308 100%	311 100%	619 100%
Week 6-8	300 97.4%	304 97.7%	604 97.6%
Week 14-16	300 97.4%	301 96.8%	601 97.1%
Month 12	294 95.4%	300 96.5%	594 95.9%
Month 18	293 95.2%	298 95.8%	591 95.5%
LFU over 18 mos.	4.8%	4.2%	4.5%

Inherent Limitations of Statistical Methods Used to Address Missing Data

- ✓ Missing Data frequently are due to mechanisms that create strong dependent censoring
- ✓ These mechanisms can be related to:
  - ➢ occurrence of 'off target' effects of interventions
  - ➢ participant willingness/ability to return for evaluation
  - ➢ inherent frailty of the participant
- ✓ Covariates that are both known and recorded usually are only the tip of the iceberg for the totality of factors that explain important inherent differences between participants with vs. without missing data

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"Non-adherent" 40%						
Followed	-	-	-	-	-	-
LFU	40%	1	35%	40%	1	35%

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% PY LFU	25%	30%

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Observed HIV Rate	24.0%	

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AT 2 YEARS

Actual HIV Rate	26%	26%
% PY LFU	25%	30%
Observed HIV Rate	24.0%	15.7%

$p < .001$

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% PY LFU	25%	30%
Observed HIV Rate	24.0%	15.7%

$p < .001$

	Control Regimen		Microbicide	
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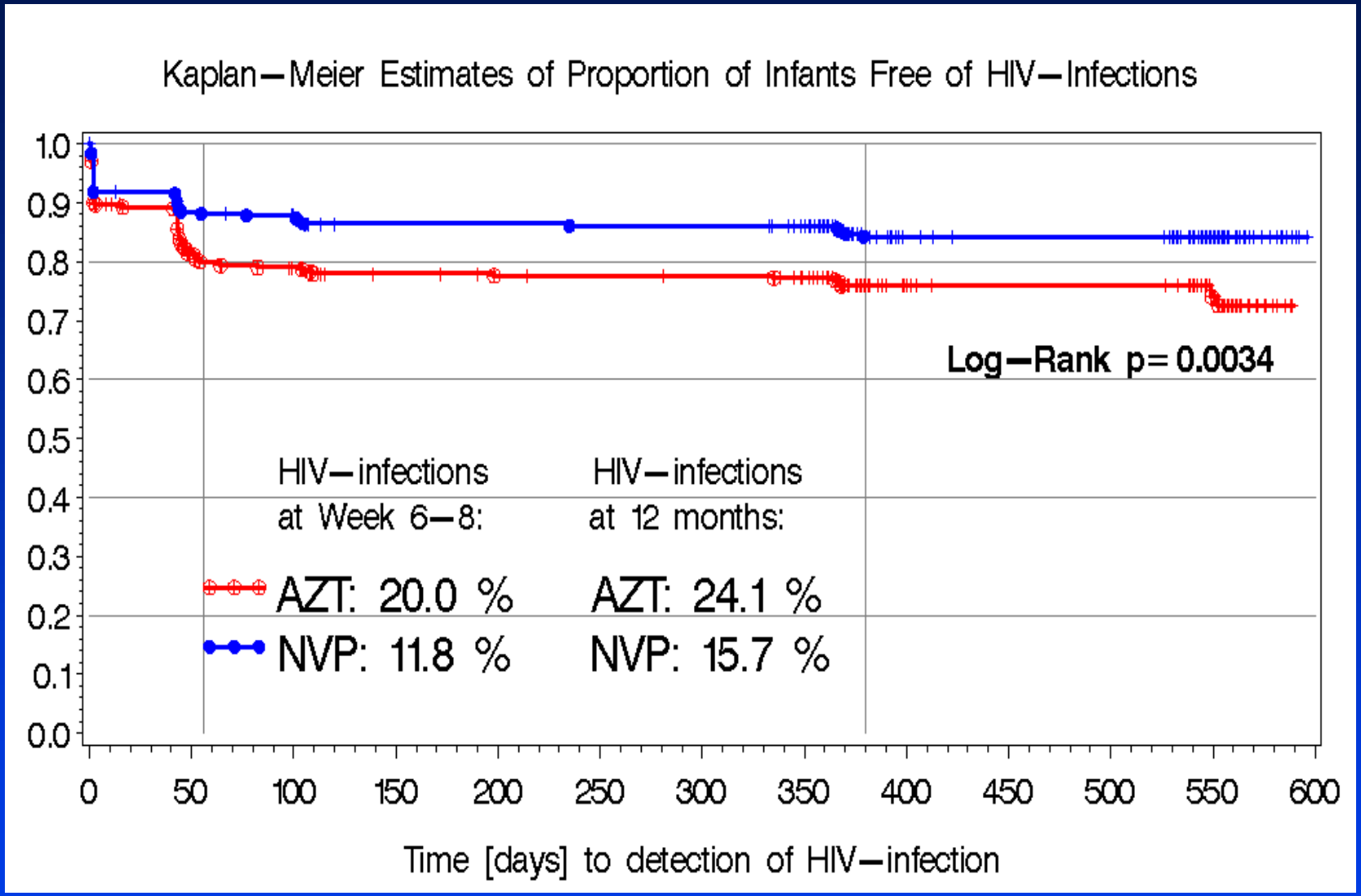
AT 2 YEARS

Similar percentages of missing data do not eliminate concern about bias

% PY LFU	25%	30%
Observed HIV Rate	24.0%	15.7%

$p < .001$

HIV TRANSMISSION THROUGH 18 MONTHS



Summary

It is important to pursue many approaches to reduce the occurrence of missing data:

✓ Protocols should more clearly distinguish between reasons for taking a patient '*off study treatment*' (i.e., non-adherence) versus '*off study*' (i.e., non-retention).

✓ Follow-up should not be discontinued due to inappropriate characterization of '*withdrawal of consent*'.

✓ The informed consent process should more clearly alert patients to the negative impact that incomplete capture of outcomes has on trial integrity and credibility.

✓ Protocol specified increases in sample sizes to address missing data should be recognized to simply produce *more precise biased* estimates.

Summary

✓ Studies should involve only those investigators who are committed to follow all patients until death or capture of all trial outcomes, even if the patients have discontinued randomized treatment or initiated other interventions…

& proper reimbursement should be provided for such efforts.

✓ Protocols should specify performance standards for achieving high quality of trial conduct, including high levels of data capture

✓ Creative and effective procedures should be implemented during enrollment and follow-up to enhance achieving pre-specified targeted levels of retention.

✓ An oversight process should be in place during trial conduct to ensure the achievement of performance standards, including targeted levels of data capture.

Oversight Process: "Study Monitoring Committees"

- ✓ Goal: Improve the implementation of creative procedures for enhancing the quality of trial conduct
- ✓ Regular Oversight by Peer Reviewers during trial conduct

  …*semi-independent* membership that includes network researchers without leadership responsibilities in the trial
- ✓ Access only to data *pooled* across intervention groups regarding measures of Quality of Trial Conduct
- ✓ Activities:
  - Assess whether pre-specified targets for performance are met for key measures re. Quality of Trial Conduct
  - Make recommendations to Study Team and the DMC regarding steps to be implemented to improve these rates.

(DMC denotes the *independent* 'Data Monitoring Committee')

Approaches to Avoid

✓ Changing the definition of a primary end point to reduce the risk for missing data if such a change meaningfully compromises the end point's clinical relevance.

- Reducing the follow-up period in chronic disease settings when longer term benefit-to-risk profile is key
- The end point based on the composite of events, "*progression of major symptoms*" and "*death*", forming a broader composite that also includes the events, "*treatment discontinuation*" or "*exposure to rescue Rx*"

✓ Compromising clinical relevance:

…an unacceptable price to pay to reduce informative missingness that occurs through failure to follow patients after they have discontinued randomized interventions.

Some Perspectives on Addressing Missing Data in Clinical Trials

Key Conclusion:

The preferred approach to handling missing data:

- ✓ **Prevent missing data,**
  by obtaining outcome evaluations
  in all surviving patients
  who haven't withdrawn consent
- ✓ Use imputation methods widely understandable and based on rational pre-specified assumptions

Principles & Insights

Given the lack of satisfactory approaches to “treat” missing data…

Principles & Insights

"An Ounce of Prevention Is Worth a Pound of Cure"

* NRC, 2010. "*The Prevention and Treatment of Missing Data in Clinical Trials*". Washington DC. National Academies Press

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