Platform Trial Designs for Sequential Treatment Evaluation

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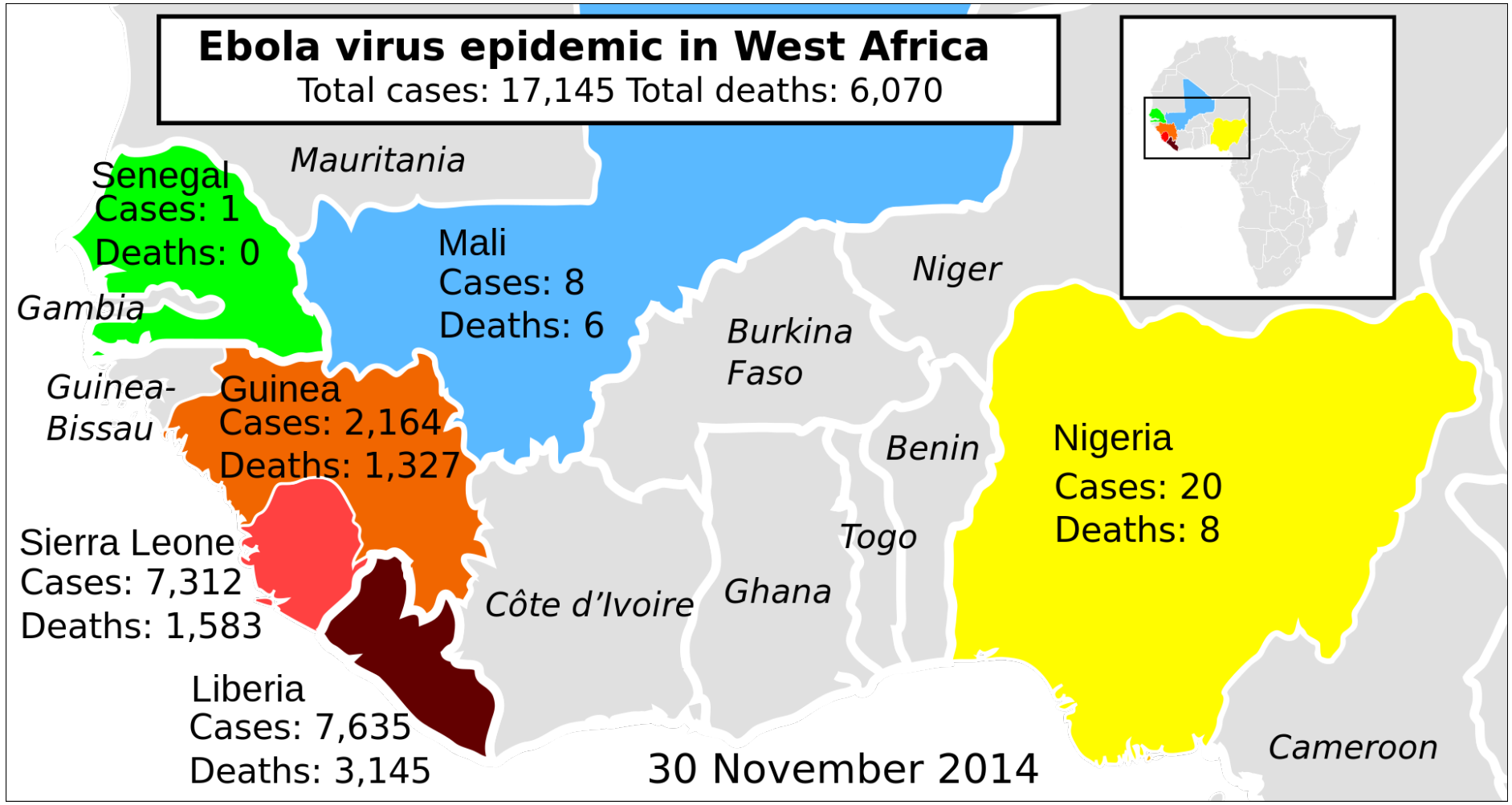
Decision Quality Framework

- We will work through the decision quality framework to motivate our decision to use a platform trial design

Source: https://go.mccombs.utexas.edu/TEE-BLG-Strategic-Decision-Making.html

Motivating Case Study:
West Africa Ebola Virus Disease Outbreak



Relevant and Reliable Information

- No approved interventions existed prior to outbreak
- Uncertainty how the epidemic would evolve
- High mortality (>70%) early in outbreak
- Variable public health and research infrastructure throughout West Africa
- Need to generate robust evidence through randomized controlled clinical trials

Appropriate Frame

- **Objective:** identify a therapy or vaccine for treating Ebola virus disease as quickly as possible from multiple candidates
- **Trial Outcome:** 28-day mortality given high rates of mortality initially observed

Clear Values and Tradeoffs

Efficiently use limited sample sizes to:

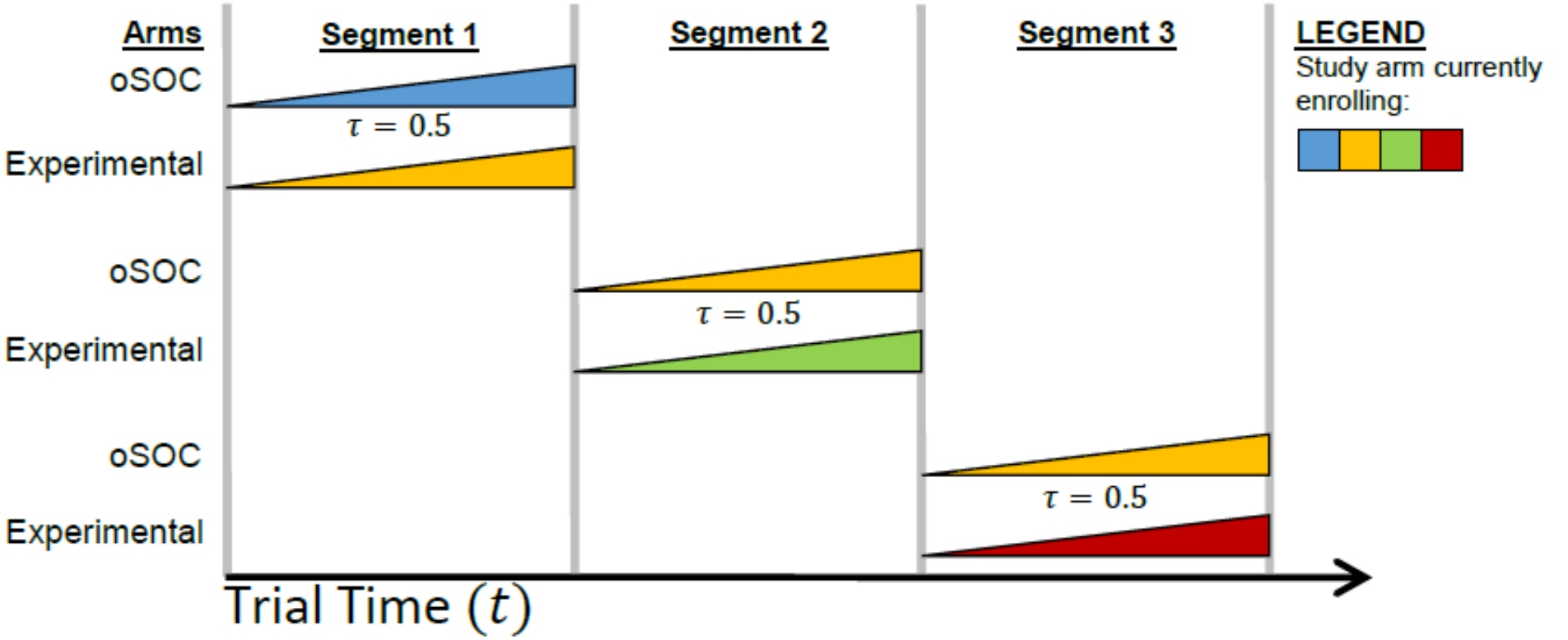
- Maximize *statistical power*
  - i.e., the probability we will identify an effective intervention in the study if it exists
- Minimize *type I error rate*
  - i.e., the probability we identify an intervention as effective when it has no effect
- Reduce *bias*
  - i.e., how much we over- or under-estimated the true effect

"Traditional" Approach to Trial Design

- Allow for creation of separate trials from different sponsors
- Limited collaboration, if any, across studies
- Each study may use different designs, outcomes, timelines for data collection, etc.

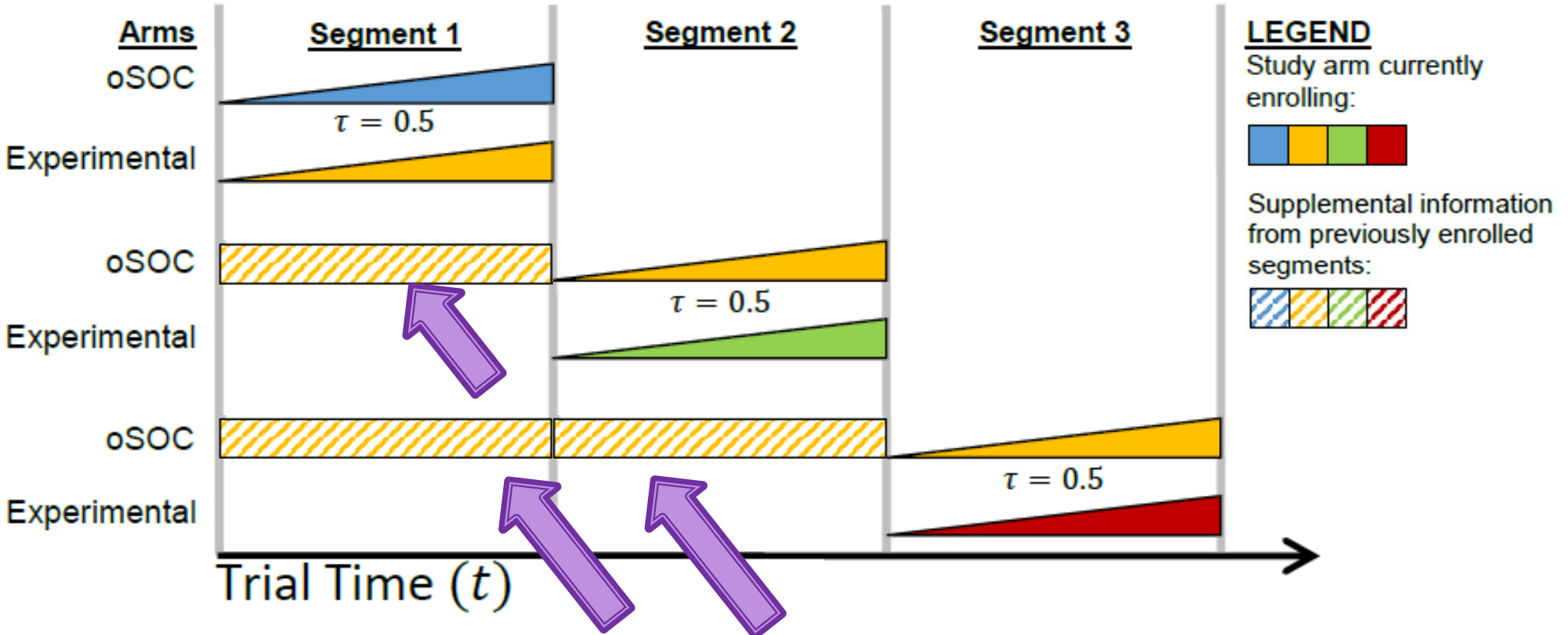
Creating Alternatives I

A sequential platform trial was ultimately proposed and implemented with the NIH to evaluate multiple candidates:



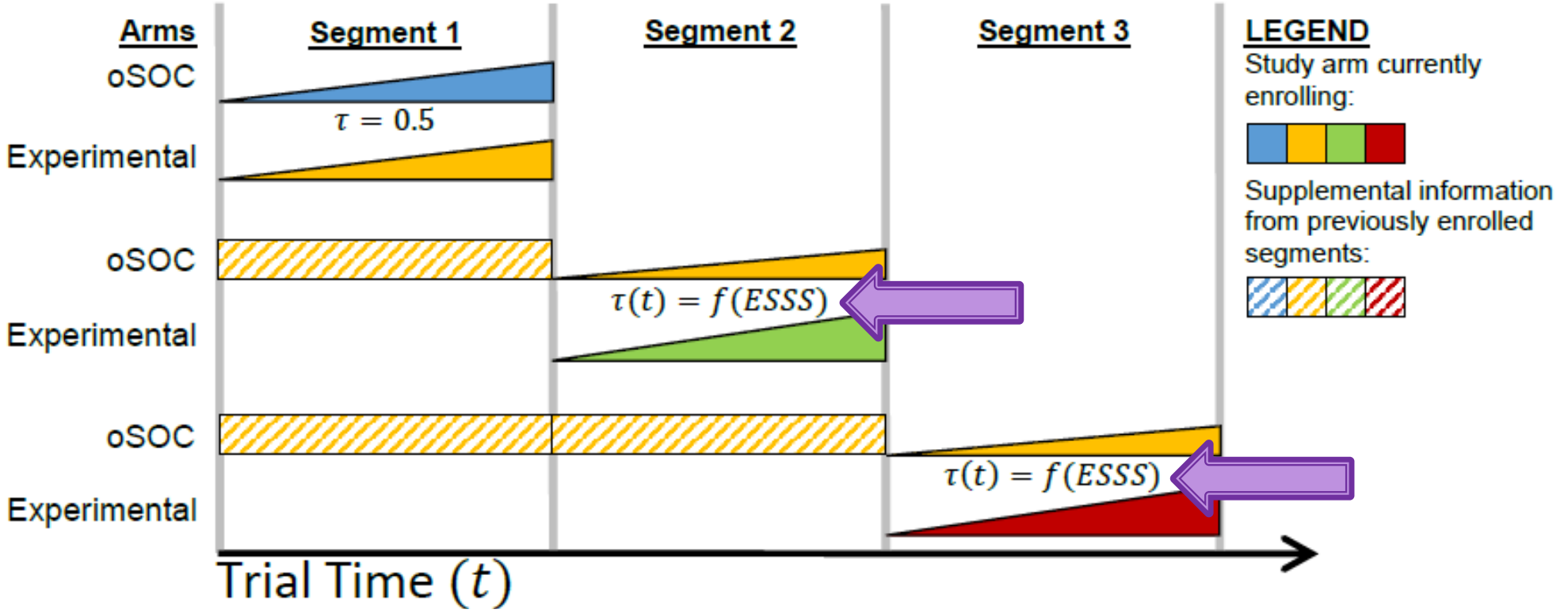
Creating Alternatives II

However, we could **incorporate past segments of data** in the analysis to more efficiently use our limited sample size:



Creating Alternatives III

Finally, we could also incorporate **adaptive randomization** to assign more individuals to novel trial arms:



Sound Reasoning (and Tradeoffs)

If we assume constant mortality over time:

NIH design: can achieve desired type I error rate, but may have low power

+ Information Sharing: can both lower type I error and increase power relative to NIH design with little bias

+ Adaptive Randomization: can also allocate more individuals to the potentially effective treatment arm

Sound Reasoning (and Tradeoffs)

If we assume decreasing mortality over time:

NIH design: can achieve desired type I error rate, but power decreases greatly as mortality decreases

+ Information Sharing: increased power and type I error rate, potential for bias from past segments

+ Adaptive Randomization: will still allocate more individuals to the potentially effective treatment arm

Commitment to Action (Trial Results)

- NIH trial terminated early due to success of public health measures, which prevented desired enrollment of 100 per arm in first segment
- Patients in treatment arm had lower 28-day mortality rate (22% vs. 37%), but it did not meet the prespecified statistical threshold for efficacy
- Did demonstrate minimal safety concerns with the intervention

General Lessons Learned

- Information sharing can increase efficiency, but may also introduce bias
- Trade-offs in performance (i.e., bias, power, type I error rates) may be more acceptable in different contexts (e.g., chronic disease vs. epidemic)
- Designs considered do improve upon inefficiencies in traditional clinical trial design

Sources

- Dodd, Lori E., et al. "Design of a randomized controlled trial for Ebola virus disease medical countermeasures: PREVAIL II, the Ebola MCM Study." *The Journal of infectious diseases* 213.12 (2016): 1906-1913.
- Kaizer, Alexander M., Brian P. Hobbs, and Joseph S. Koopmeiners. "A multi-source adaptive platform design for testing sequential combinatorial therapeutic strategies." *Biometrics* 74.3 (2018): 1082-1094.
- Hobbs, B. P., Carlin, B. P., & Sargent, D. J. (2013). Adaptive adjustment of the randomization ratio using historical control data. *Clinical Trials*, *10*(3), 430-440.

Questions?