Example #1

- Drug X1
  - Active only for *P. aeruginosa*
  - Detailed[1] insight into microbiology, PK-PD, and dose justification
- Pivotal program
  - Study #1: Prospective, randomized, open-label study of Drug X1 vs. BAT[2] across multiple body sites (Y1, Y2, Y3). N ≅ a few hundred (?)
    - Limited ability to go beyond simple descriptive statistics. Key will be case quality (real infections, sick patients) and cross-site pattern of response
  - Study #2: Open-label study of Drug X1 (companion salvage study for #1)
  - Study #3: Observational study of (inadvertently) ineffective therapy for the target pathogen (estimates placebo effect, reference point for interpreting Study #1)
  - Throughout: Use any available patient enrichment tools (rapid tests, etc.)
- Label that results
  - Drug X1 is indicated for infections at *(Y1, Y2, Y3)* due *(P. aeruginosa)*
    - *Includes language explaining limited dataset and need for careful use*

[1]Mechanism of action understood, animal models reasonably mimic human disease at relevant sites, exposure-response in the animal studies informs human dose with adequate margin. [2]BAT = Best Available Therapy, standardized insofar as possible. [2]Might use existing data (e.g., Tigecycline PK-PD analysis in HAP-VAP [Ambrose AAC 56:1466, 2012] provides a clear PK-PD estimate of placebo response rates) or pharmacometric proof from Study #1.

Example #2

- Drug X2
  - Active vs. MDR Enterobacteriaceae, equally active vs. non-MDR strains
  - Detailed[1] insight into microbiology, PK-PD, and dose justification
- Pivotal program
  - P3 study of X2 vs. standard comparator
    - Single body site Y1, standard study design parameters (endpoints, margins)
      - Intended to show drug's effectiveness in treating serious infection
      - No expectation of enrolling (any) MDR strains but because susceptibility (and thus, PK-PD math) is the same as for non-MDR strains, the results show relevant efficacy
  - Open-label study of X2 for infections due MDR strains
    - Body sites include Y1 but also sites Y2 and Y3
    - Analysis limited to simple descriptive statistics. Key will be case quality (real infections, sick patients) and cross-site pattern of response
  - From both studies: PK data (at site if possible) to show comparable exposures
- Label that results
  - Drug X2 is indicated for infections at site Y1 due *(list of pathogens)*
  - Drug X2 is indicated for infections at sites *(Y1, Y2, Y3)* due *(MDR list)*
    - *Includes language explaining limited dataset and need for careful use*

[1]Mechanism of action understood, animal models reasonably mimic human disease at relevant sites, exposure-response in the animal studies informs human dose with adequate margin.