Exploration of a Potential DOOR Endpoint for Complicated Intra-Abdominal Infections Using Nine Registrational Trials for Antibacterial Drugs

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Introduction

Desirability of outcome ranking (DOOR) utilizes an ordinal ranking system to evaluate global outcomes in clinical trial participants by incorporating safety and efficacy assessments into a single endpoint. Here, we derived and applied a DOOR endpoint to registrational trials for complicated intra-abdominal infection (cIAI).

Methods

Application of *a priori* DOOR prototype

FDA identified 6 NDAs for cIAI submitted between 2005-2019 → Nine clinical trials (n=5022 participants) → Utilized clinical data to evaluate components of *a priori* DOOR prototype → Clinical response; Infectious complications (ICs); Serious adverse events (SAEs)

Derivation, Application and Analysis of cIAI-specific DOOR Endpoint

- Created and applied cIAI-specific endpoint
- Assigned each trial participant a DOOR rank
- For each trial, estimated the DOOR probability of a more desirable rank in the treatment arm, and assessed treatment effects on endpoint components

Results: Derivation of cIAI-specific DOOR Endpoint

Table 1. cIAI-specific DOOR Endpoint

Component Events	Definition	DOOR Rank	Alive?	# of Component Events?
Absence of Clinical Response	Includes outcomes of clinical failure or indeterminate as assessed by the investigator at the TOC visit. If the participant was reviewed by the SRP, the SRP's clinical assessment prevails.	**0**	Yes	0 of 7
Infectious Complications	Newly identified infection that was not initially diagnosed at the start of the trial, **including those related and unrelated to the original cIAI.**	**1**	Yes	1 of 7
		2	Yes	2 of 7
Procedures	**Any additional abdominal intervention, to include surgical, percutaneous, or endoscopic procedures, that the participant has after their first operation for cIAI.**	**3**	Yes	3 of 7
		4	Yes	4 of 7
	Any post-operative wound related surgical or percutaneous intervention that the participant has after their first operation for cIAI.	**5**	Yes	5 of 7
		6	**Yes**	**6 of 7**
		7	**Yes**	**7 of 7**
Serious adverse events	Includes SAEs as defined by the Code of Federal Regulations 21CFR312.32[a, b]	**8**	**No**	**Any**

*Blue, bolded text indicates modification from *a priori* DOOR prototype. [a]Any medical event that: 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, or 5) is a congenital anomaly/birth defect. [b]If a serious adverse event is also in the infectious complication component, this will count as two events for the DOOR rank. **Abbreviations:** TOC, test of cure; SRP, Surgical Review Panel; cIAI, complicated intra-abdominal infection; SAE, serious adverse event; DOOR, Desirability of Outcome Ranking.

Results: Component Analysis

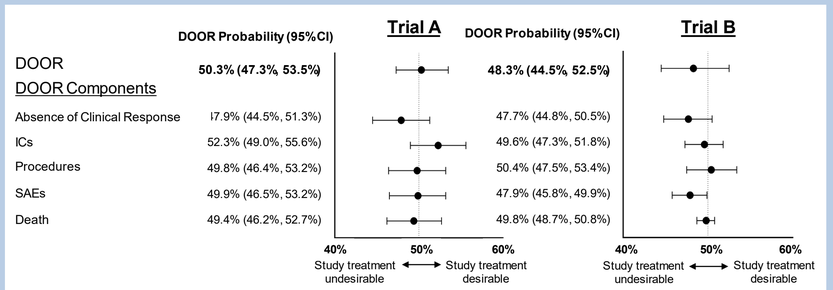

Figure 3. Forest plot of the DOOR probabilities for DOOR and for each DOOR component. Trial A has no significant differences between treatment arms in the component analysis (Left). The study treatment was shown to be nominally statistically inferior for SAEs in Trial B (Right).

Results: Summary

- Participants with poorer clinical outcomes experienced more infectious complications, serious adverse events and procedures (Fig. 1).
- The *a priori* DOOR prototype was modified to capture additional clinically relevant events experienced by trial participants (Table 1).
- DOOR distributions between treatment arms were similar within trials, though they differed across trials (Fig. 2).
- Component analyses enabled more detailed evaluation of risks vs. benefits between treatment arms (Fig. 3).

Conclusions

- We derived and applied a novel, disease-specific DOOR endpoint that may better characterize participants' overall outcomes in the trial environment.
- Performance of this endpoint should be evaluated prospectively as a secondary endpoint in Phase 2 or 3 trials.

Results: Participant Experiences by Clinical Response

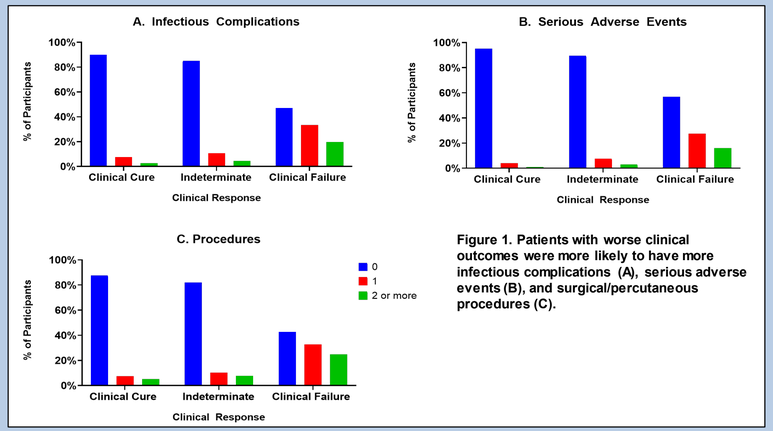

Figure 1. Patients with worse clinical outcomes were more likely to have more infectious complications (A), serious adverse events (B), and surgical/percutaneous procedures (C).

Results: DOOR Distribution Using cIAI-specific Endpoint

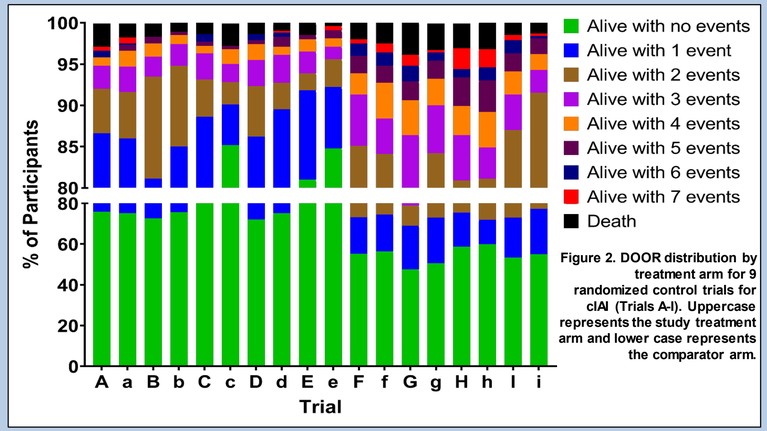

Figure 2. DOOR distribution by treatment arm for 9 randomized control trials for cIAI (Trials A-I). Uppercase represents the study treatment arm and lower case represents the comparator arm.

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