Analysis Planning and Interpretation Using Causal Directed Acyclic Graphs: A Case Study in Oncology

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Introduction

Background

Trends in clinical and regulatory science increasingly favor approaches to decision making based on the totality of evidence.[1] The Quantitative Data Integration to Enhance Clinical Trials (QUIC) initiative at Boehringer Ingelheim was established in order to foster study designs and analyses consistent with this emphasis on evidence integration. In relation to study design, emerging guidance for the use of real world evidence (RWE) is in many cases pertinent for all evidence integration efforts, even those that do not involve RWE. This is the case because the beneficial effects of randomization are generally nullified when multiple data sources are combined, rendering such analyses effectively observational in nature. Given this inherently observational (non-randomized) evidential framework, multiple guidance documents have emphasized the importance of causal directed acyclic graphs (DAGs) to assess the fitness for purpose of study designs.[2]

Objectives

- **Original objective:** to conduct a proof of concept exercise to evaluate the utility of causal DAGs for the planning of analyses that were anticipated to leverage RWE.
- **Modified objective:** to illustrate the utility of a causal DAG as an aid in the interpretation of a non-randomized comparison from a Phase 1 oncology trial.

Methods

Potential candidates for the desired proof of concept were evaluated across a range of development programs in multiple therapeutic areas (results not shown). An oncology program for a second-line / third-line indication was identified as having the potential to benefit from supplementary analyses based on a real world data (RWD) database. Specifically, results from a Phase 1 study in this program suggested that the efficacy of the novel agent might vary as a function of treatment history, and analyses of the RWD were proposed to evaluate the plausibility of this effect modification hypothesis. In order to support the planning for this RWE-based analysis, a causal DAG was developed in consultation with subject matter experts, using the DAGitty web application at `www.dagitty.net`.[3]

Review of (Anonymized) Prior Results

Treatment History		Ph.1 Treatment	ORR
targeted (1L)	chemo (2L)	Novel Tx (3L)	25%
	targeted+chemo (combo 1L)	Novel Tx (2L)	15%

Table 1: Baseline patient disposition and (fictionalized) overall response rates (ORR) for a Phase 1 oncology trial. ORR varied as a function of treatment history (25% for sequential therapy versus 15% for combination therapy), perhaps suggesting that patients' ability to respond to the novel treatment was modified by treatment history.

Results

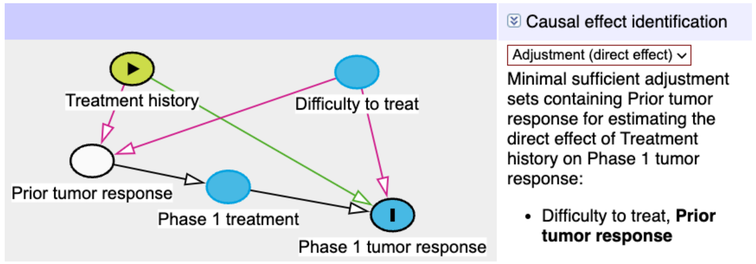

Figure 1: Causal directed acyclic graph (DAG) developed in consultation with subject matter experts. Treatment history was the explanatory variable of interest within this line of inquiry and so was selected as the "exposure" variable (indicated by green color). Prior tumor response is a "collider" in this DAG because more than one arrow points into this node. The Phase 1 study design required conditioning on this variable (indicated by depicting the node in white, corresponding to the fact that only subjects who had failed prior therapies were enrolled), thereby opening up a "backdoor path" (the pathway consisting of the red lines, without regard to the directionality of the arrows) and inducing a phenomenon known as "collider bias", which is a specific type of selection bias.[4] The DAGitty web application was used to interactively develop the graph, and also to analyze it: the "causal effect identification" panel to the right indicates that the collider bias would be eliminated in an analysis that provided adequate covariate adjustment for "difficulty-to-treat".[3]

Discussion

- The "collider bias" revealed by the DAG-based analysis essentially offers a competing explanation for the prior results shown in Table 1: the difference in ORR between the two "arms" would be expected even in the absence of effect modification, simply as the result of differential enrichment (e.g., patients who had failed prior combination therapy might have been already more difficult to treat at the beginning of the Phase 1 study).
- In the absence of any compelling evidence favoring an effect modification hypothesis, the previous plans for an RWD-based supplementary analysis were abandoned.
- The original intent of the DAG-based analysis was to suggest *how* to effectively analyze the RWD. As it turned out, the actual value of the DAG-based analysis in this case was to suggest that investment of resources in an RWD-based analysis was not warranted at all. This *did* illustrate the value of DAGs for analysis planning, albeit in an unexpected way.

Conclusion

The utility of causal DAGs is not limited to specialized problems involving RWE and is not limited to prospective assessments of fitness for purpose. This case study provides one data point to suggest that both prospective planning and retrospective interpretation for any non-randomized comparison can be elucidated with the help of causal DAGs.

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