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TRIALS AVOID HIGH RISK PATIENTS AND UNDERESTIMATE DRUG HARMS

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We are thankful to Daniel Park and Brendan Balthis for their expert research assistance. We are grateful for Christopher Manz and Hari Raman for their thoughtful guidance on how to classify oncology trials and identify trial-eligible cohorts in SEER-Medicare data. We thank David Chan and seminar participants at University of Massachusetts- Amherst for their helpful feedback on this project. Sachin Shah received grant funding from NIA K76AG074919 to support this work. This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement NU58DP007156; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute, the National Bureau of Economic Research, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors.

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ABSTRACT

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Trials Avoid High Risk Patients and Underestimate Drug Harms

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Abstract

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*__Abaluck:__ Yale University and the National Bureau of Economic Research __Agha:__ Harvard University and the National Bureau of Economic Research. __Shah:__ Massachusetts General Hospital and Harvard University. We are thankful to Daniel Park and Brendan Balthis for their expert research assistance. We are grateful for Christopher Manz and Hari Raman for their thoughtful guidance on how to classify oncology trials and identify trial-eligible cohorts in SEER-Medicare data. We thank David Chan and seminar participants at University of Massachusetts-Amherst for their helpful feedback on this project. Sachin Shah received grant funding from NIA K76AG074919 to support this work. This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement NU58DP007156; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors.

1 Introduction

Randomized controlled trials evaluating new drugs are intended to provide safety and efficacy evidence to inform regulatory and clinical decisions. But, if trial enrollees are not representative of the population that ultimately takes up treatment, trials may fail to generate externally valid findings needed to inform drug approval decisions and treatment choices. FDA efforts and academic evaluations of trial representation have focused on demographic dimensions (such as sex, race, and age), but treatment effects are more closely tied to clinical comorbidities and frailty than these broad demographic categories.[1]

In this paper, we study whether older patients at high risk of drug-induced serious adverse events (SAEs) are underrepresented in cancer drug trials. SAEs are a crucial determinant of heterogeneity in the net benefits of drugs. Cancer drugs often have toxic side effects, such as dangerous infections and organ failure. These side effects limit the efficacy of treatment by forcing early discontinuation of treatment, preventing patients from receiving the therapeutic dose, and causing premature deaths (Muss et al., 2007; Hurria et al., 2011; Shah et al., 2020). Yet, current trials may underestimate these SAE harms. Approximately one-third of all novel therapies approved between 2001 and 2010 had a post-market FDA safety event (i.e., boxed warning, FDA safety communication, or withdrawal) (Downing et al., 2017), raising questions about whether current approaches to trial regulation are adequate to surface relevant safety information at the time of drug approval.

To evaluate the external validity of drug safety findings in trials, we need to compare SAE treatment effects in trials to SAE treatment effects in the target population. Trials measure and report adverse events in ways that are often poorly documented, inconsistently defined across trials, and difficult to replicate in large administrative datasets (Sivendran et al., 2014), precluding direct comparison of SAE rates in trials versus observational data. Trials also fail to collect systematic data on patient comorbidities and other important SAE risk factors. For these reasons, we develop our own estimates of how SAE rates vary depending on patient risk factors, using data where we

[1] For recent regulatory measures and consensus reports on trial representativeness, see: National Academies of Sciences, Engineering, and Medicine (2022); Food and Drug Administration Oncology Center of Excellence, Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research (2022); *FDA Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data* (2014).

observe both the target population and trial participants.

Our analysis proceeds in three steps using data from the Surveillance, Epidemiology, and End Results (SEER) Program linked to Medicare claims, as well as trial information from ClinicalTrials.gov. First, we predict SAEs in the first three months following initiation of cancer drug treatment using patient characteristics. Second, we demonstrate that this model of SAE risk systematically predicts heterogeneity in SAE treatment effects, using a quasi-experimental approach leveraging staggered timing of treatment initiation after cancer diagnosis. Third, we find that trial-enrolled patients have lower predicted SAE treatment effects, compared to the target population.

To construct predictions of SAE risk, we identify a cohort of patients who initiate treatment with cancer drugs within 6 months of diagnosis and measure hospitalizations with a primary diagnosis code indicating a potential SAE. We predict each cancer patient's risk of hospitalization for a potential SAE after treatment initiation given their comorbidities, frailty, and age. We use a jackknife approach to develop SAE risk measures for each patient from a model that was estimated excluding data from the index patient.

Next, we exploit variation in the exact timing of treatment initiation relative to cancer diagnosis to estimate SAE treatment effects. Using an event study framework that compares treated individuals to not-yet-treated comparisons, we identify the effect of initiating treatment on SAE, controlling for time since cancer diagnosis, as well as the patient's cancer type and stage at diagnosis. Treatment initiation with a cancer drug leads to a large and sudden spike in the SAE rate, increasing a patient's monthly risk of hospitalization due to an SAE by 2 percentage points. We then relate treatment effects to (jackknifed) risk, finding that SAE treatment effects are much larger for higher-risk patients: patients in the top third of the risk distribution experience twice as large an increase in SAE rates as patients in the bottom third. Our measure of SAE risk thus predicts substantial heterogeneity in the effect of cancer drug treatment on SAE hospitalizations.

Following this, we identify trial participants in SEER-Medicare data and compare them to non-participants. This approach allows us to investigate trial selection patterns within a fixed subpopulation. We ascertain trial participation using a newly validated method that leverages National Clinical Trial (NCT) identifiers reported in Medicare claims (Green et al., 2022b). A

single trial generally tests a single drug for a target population and is intended to be informative about the treatment benefits and harms in that target population (not all off-label indications for which a drug might be prescribed). Thus, we aim to benchmark trial representation using the target population of patients stated by the trialists themselves. To identify each trial's target population, we match each trial participant to the public NCT record in the ClinicalTrials.gov database, and identify the cancer type, stage, treatment line, and relevant tumor markers targeted by the trial. Under the guidance of a practicing oncologist, we identify cohorts of patients in registry-linked claims data that matched the relevant trial's target population. The inclusion of cancer registry data allows us to identify stage at diagnosis and certain tumor markers, while claims data allow us to infer treatment line (i.e., first vs. second drug treatment regimen) and disease progression (based on subsequent treatment choices following diagnoses). Together, these data allow us to compare trial participants to non-participants who would be eligible for the treatment.

Finally, we compare SAE risk among trial enrollees to SAE risk among the broader set of patients eligible for each treatment being evaluated. Patients at the 10th percentile of the SAE risk distribution are 4 times more likely to be enrolled in a clinical trial compared to patients at the 90th percentile. This pattern arises even among patients receiving active drug treatment for advanced stage cancer, and thus does not reflect a general unwillingness to offer systemic treatment to frailer patients. Results are very similar in magnitude when we restrict attention to industry-funded, Phase 3 trials, which are typically the pivotal trials on which FDA decisions are based. Our findings suggest that clinical trials systematically underestimate the adverse event risks associated with tested treatments by under-enrolling patients whose comorbid conditions and frailty increase their risk of adverse events. On average, the target population has 14% higher predicted SAE treatment effects compared to trial enrollees.

Our sample is limited to Medicare beneficiaries aged 65+ and thus most germane to considering the external validity of cancer trial results for older patients. When considering the implications of this finding for the overall external validity of trials' average treatment effects, our estimate is likely to understate the full gap since SAE risk increases with age. A majority of incident cancers occur in patients over 65 years old (National Cancer Institute, 2026), but these patients are

underrepresented in cancer trials (Ludmir et al., 2019; Lewis et al., 2003) suggesting that clinicians and regulators have to extrapolate findings on (presumably lower-risk) under-65 trial enrollees to (presumably higher-risk) over-65 enrollees.

The standard regulatory approach to evaluating the safety of drugs for older patients has relied on age-based subgroup reporting. FDA regulations require sponsors to present safety and effectiveness data by age, and drug sponsors have typically complied by reporting comparisons for patients aged 65 and older (U.S. Government Accountability Office, 2007). Our results show that subgroup analyses produce systematically understated estimates of SAE treatment effects for older patients, and are thus inadequate for assessing whether trial evidence generalizes to this population. We also show that the FDA's current goal of increasing enrollment of older patients (focused on ages 75+) to improve age representation of trial enrollees would not be sufficient to close the gap (Food and Drug Administration 2022).

The external validity of trial-estimated SAE treatment effects is crucial for informing both FDA policy action and individual clinical decisions. Our empirical analysis focuses on SAEs because these outcomes are observed in claims data and occur soon after treatment initiation, making them well suited to our staggered treatment timing design. By contrast, the primary efficacy endpoints in many cancer trials require longitudinal tumor information unavailable in claims and typically accrue over longer horizons than our design can credibly identify. We therefore estimate the external validity of drug-induced SAEs and use a model to connect this object to the broader benefit-risk calculus.

The classical model of trial enrollment shows that representative trials minimize the mean squared error of the estimated average treatment effects in the target population (for both benefits and harms). But regulating representativeness is challenging, given that there are many possible dimensions of heterogeneity to consider. We derive formal conditions under which regulation requiring representativeness in terms of average SAE risk also improves representativeness in terms of net impacts, taking into account both the drug's therapeutic benefit and induced harms.

Our insights could inform a new regulatory framework aimed at improving trial representativeness for harms. This would involve: (1) pre-trial reporting of the anticipated target population,

(2) reporting of predicted risk of trial enrollees' adverse events relative to this benchmark population (using a risk model such as the one we develop here), and (3) post-marketing surveillance to assess the correspondence between the prespecified target population and use of the drug for the indication in question.

We estimate that correcting SAE bias in cancer clinical trials would generate welfare gains of about $350 million per year for oncology drugs. These gains arise primarily through improving physician-patient treatment decisions: corrected SAE estimates raise the harm component of the treatment decision and would reduce treatment among patients whose expected mortality benefit is close to, but below, the added SAE cost. This channel is consistent with evidence that treatment toxicity is consequential for patient preferences; for example, 42% of cancer trial participants report that they would not accept six months of chemotherapy for two months of added survival (Vaz-Luis et al., 2017). In contrast, relatively few drugs appear close enough to the approval threshold for corrected SAE estimates to change FDA approval decisions, making this channel much smaller under our central assumptions.

An extensive clinical literature has considered the differences between efficacy in trials and effectiveness in clinical practice, often identifying gaps without isolating the underlying reasons (Nordon et al., 2016; Visram et al., 2023; Agha et al., 2023). Recent research has begun to consider the role of trial enrollment patterns as a potential contributor to these gaps.[2] Our paper has three primary innovations compared to the existing clinical literature on trial enrollment and adverse events. First, we quantify a relationship between SAE risk and SAE treatment effects rather than assuming that patients at higher risk of potential SAEs also experience more SAEs as a causal result of treatment. Second, we measure treatment effects in the same way for trial and non-trial enrollees (or predicted trial enrollees), enabling an "apples-to-apples" comparison.[3] Third, we observe directly which patients are in trials rather than inferring this from stated exclusion rules.

[2]See, for example: Fujimoto et al. (2023); Jain et al. (2021); Orcutt et al. (2025); Rivera-Caravaca et al. (2018); Hanlon et al. (2022); Steg et al. (2007); Kennedy-Martin et al. (2015).

[3]Our approach contrasts with studies that benchmark against outcomes reported in trials, which often have measurement differences with analogous "real-world" quantities. Identifying adverse events through chart review vs. administrative records often yields divergent results (Connolly et al., 2024). EHR and claims data do not consistently capture the patient symptoms which may signify adverse events (Nadkarni, 2010). Even when comparing results for the same clinical trial reported in different forums (ClinicalTrials.gov vs. academic publications), adverse event rates often fail to match (Tang et al., 2015; Hughes et al., 2014).

To our knowledge, existing studies address at most one of these three challenges, and typically with much smaller scope (e.g., studying one trial or a few hospitals). We show that trial enrollees have *predictably lower treatment effects* in ways that an informed regulator could assess before the trial is conducted, provided they had data on means of comorbidities in both the trial and the target population.

Recent research in economics has also considered problems related to the external validity of trials (Vivalt, 2020; Al-Ubaydli et al., 2017; Malani, 2008). Manski (2017) argues that external validity merits as much attention as internal validity when evaluating and applying medical research, given that treatment response is usually heterogeneous. In a different context, Allcott (2015) points out that selective participation in field experiments has important implications for external validity. Chassang and Kapon (2022) develop a set of best practices for improving external validity, including measuring rich covariates of trial participants. In the context we study (i.e., cancer drug trials), this best practice is rarely applied: patients' non-cancer comorbidities are not documented in trial results and only rarely collected in trial data repositories. Our efforts to surmount these obstacles shaped our specific empirical approach, but future analyses could be facilitated by richer data collection.[4]

Prior research on how financial incentives shape research investment suggests a potential explanation for the patterns we document here (Oostrom, 2024; Budish et al., 2015; Agha et al., 2022). Trial findings have large effects on prescribing decisions (McKibbin, 2023; Azoulay, 2002), implying that there are strong private incentives to produce favorable results. The patterns of nonrepresentative enrollment we have uncovered may arise if trialists want to minimize reported harms, as these adverse outcomes factor heavily into both FDA decisions (Lackey et al., 2021; Tracy, 2025) and treatment choices (Busch et al., 2014; Chintagunta et al., 2009).

Improving the representativeness of trials could have important effects on which drugs are developed and which patients choose to use them. Kao and Oostrom (2024) and Michelman and

[4]Research in biostatistics has developed transportability methods for estimating externally valid treatment effects, by reweighting trial observations to match the distribution of observable characteristics in a target population, or with doubly robust methods that also estimate treatment effect heterogeneity within trial data (Dahabreh et al., 2020, 2021; Degtiar and Rose, 2023; Robertson et al., 2024). These methods are poorly suited to our retrospective analysis of external validity, both because most trials did not systematically collect data on important predictors of SAE risk and because trials may rarely or never enroll patients at greatest risk.

Msall (2024) find that increasing clinical trial enrollment of older patients and women, respectively, fosters development of drugs to serve those populations. Alsan et al. (2024) studies the downstream consequences of nonrepresentative trials, finding that the underrepresentation of Black patients in clinical trials reduces their adoption of new drugs.

Trial findings are also a crucial input to FDA decisions. Cohen et al. (2021) and Olson (2002, 2008) found that shortening the timeline for FDA review led to the approval of drugs with worse safety profiles, while Philipson and Sun (2008) and Philipson et al. (2008) argue that FDA policy emphasizes safety at the expense of speed in approval decisions. By regulating representativeness of SAE risk among trial participants, it may be possible to surface safety information more quickly and accurately (with greater statistical power in smaller samples), lessening the potential tradeoff between speed and decision quality.

The paper proceeds as follows. Section 2 describes the clinical setting and further explains our focus on serious adverse events. Section 3 discusses the context and data. Section 4 describes methods and results estimating heterogeneous effects of cancer drug initiation on SAEs. Section 5 investigates the relationship between SAEs and trial participation. Section 6 develops a formal framework for trial representativeness and uses it to discuss a potential regulatory framework for improving representativeness and to model how trial sponsors may respond. Section 7 concludes.

2 Context: Generalizability of Cancer Trials

The external validity of cancer trials is a particularly salient problem for the care of older adults with cancer, who comprise a majority of incident cancer diagnoses (National Cancer Institute, 2025). High rates of comorbid disease among older adults complicate treatment choices; over two-thirds of Medicare beneficiaries have two or more chronic conditions and more than one-third have 4 or more conditions (Lochner and Cox, 2013). Concerns about drug safety, often framed as tolerability, are a major barrier to treating older adults with cancer, who are less likely to initiate treatment, more likely to discontinue treatment early, and more likely to experience SAEs due to chemotherapy.[5]

[5]See Bradley et al. (2008); Dy et al. (2006); Luo et al. (2006); Pasetto et al. (2008); O'Grady et al. (2011); Vinod et al. (2010); Neugut et al. (2006); Grønberg et al. (2010); Hassett et al. (2011); Zauderer et al. (2009).

Limited trial generalizability has been a long-standing concern of both physicians and regulators. In 2020, FDA guidance established that clinical trials should be designed to be "representative of the population that will use the drug if approved" (U.S. Food & Drug Administration, 2020). This guidance was further operationalized in June 2024 when the FDA released draft guidance requiring trial sponsors to submit goal patient enrollment disaggregated by age group, sex, and race and ethnicity (U.S. Food & Drug Administration, 2024). Stated goals must be justified, for example, based on the disease distribution by demographic group. However, demographic variables, including age, race, and sex, do not capture many of the most clinically-relevant considerations. Comorbidities and geriatric syndromes (e.g., frailty, disability) are key features that influence physician decision-making (Sarfati et al., 2016; George et al., 2021). The current regulatory approach has neglected to provide guidance for measuring or ensuring that trials represent the distribution of clinical risk factors among patients who would use the drug.

In this paper, we focus on the external validity of drug trials for estimating the SAE rates associated with new drugs. Though our focus on SAEs is partially born out of empirical limitations, it also reflects the leading concern about cancer drug appropriateness for older patients. Surveys of cancer clinical trial participants showed that adverse events severely limit the acceptability of treatment: 42% would not accept 6 months of chemotherapy for 2 months of added survival (Vaz-Luis et al., 2017). Generating accurate estimates of SAE treatment effects is important to ensure patients receive preference-concordant care.

We use a quasi-experimental approach leveraging staggered timing of treatment initiation to estimate adverse event treatment effects. Because SAEs peak within a few weeks of treatment initiation, our event-study framework is well-suited to identifying SAE treatment effects. In contrast, the benefits of cancer treatment accrue further in the future, and the most common trial endpoints are unobserved in claims data. Most cancer drug trials measure treatment benefits using endpoints such as progression-free survival, disease-free survival, or objective response rate; measuring these endpoints requires information on changes in tumor size and metastasis over time.[6] While the SEER data provide detailed information on tumors at the time of diagnosis, they do not include

[6]Only 41% of trials in our sample report overall survival as a primary outcome, which is consistent with other recent analyses of trial endpoints Teuwen et al. (2023).

longitudinal information about cancer recurrence or progression. Likewise, Medicare claims data do not permit tracking of tumor progression and recurrence. Thus, we are missing the data needed to capture the primary outcomes for most trials.

Overall survival is observed in our data, but our quasi-experimental variation is poorly suited to analyzing this outcome for two reasons. First, in our staggered treatment timing design, patients who are treated later have survived longer since diagnosis to arrive at their treatment date; this induces survivorship bias.[7] Second, the benefits of treatment typically accrue over many months or years, and our research design leverages small variation in the timing of treatment initiation; thus, it is not well suited to estimating the long-run effects of drug treatment vs. no treatment.

3 Data Sources & Summary Statistics

3.1 SEER-Medicare data

This project uses data from the SEER Program (2014-2019) linked to Medicare claims (2013-2020) to study trial enrollment and generalizability (National Cancer Institute, 2022). The SEER Program pools data from 16 state and regional cancer registries, spanning many large states including California, New York, and Texas (see Appendix Table A7). These data capture all incident cancer diagnoses for 7 cancer types (bladder, breast, colon, lung, pancreas, rectal, renal). Using these data, we developed two distinct cohorts for the two phases of our investigation: (1) the Adverse Event Sample to identify patients at highest risk of experiencing a SAE upon initiation of cancer drug treatment and to estimate heterogeneous SAE treatment effects; (2) the Trial Participation Sample to identify how trial enrollment varies with predicted SAE treatment effects. See Appendix A1 for further details on cohort construction.

Adverse Event Sample. The first cohort was developed to estimate heterogeneous effects of cancer drug initiation on SAE risk. The cohort includes patients with new diagnoses of cancer who initiate drug treatment within 3–6 months following diagnosis. Initiation of cancer drug treatment is

[7] We demonstrate the robustness of our SAE findings to this bias by showing results are similar whether or not we condition sample inclusion on survival for the early-treated cohorts. When survival itself becomes the outcome, the problem is more acute.

identified using the first cancer drug billed to Part B or Part D claims, following the drug definitions described in Appendix A1. We exclude patients who initiate drug treatment immediately upon diagnosis, because hospitalizations ramp up around the time of diagnosis, including the month or two before diagnosis; for these patients, it is difficult to disentangle causal effect of initiating a new drug from the effects of developing cancer. (We discuss our approach to identification further in Section 4.2.) Using SEER data, we record patient's cancer type and stage at diagnosis. We require that patients be continuously enrolled in Medicare Parts A/B/D for 1 year before and after their diagnosis date (or until death, if they die within 1 year).

SAEs are measured using diagnosis codes identified by prior researchers and reviewed by clinicians on our team.[8] We require a relevant code to appear as the primary diagnosis on an inpatient hospitalization claim. Our SAE definition spans several key types of SAEs associated with cancer treatment: infection, kidney, cardiac, hematologic, gastrointestinal, liver and lung events. We measure SAE incidence at the patient-month level, defined as whether the patient had any SAE hospitalization during the month. In our baseline analysis, we retain patients in the sample even after death, and record no adverse events in months after death; in Appendix Figure A1, we show very similar findings with an alternative approach that drops patient-month observations after the patient's death. We also construct patient-level risk factors for adverse events as of the date of cancer diagnosis, including chronic conditions (as defined by the Chronic Condition Warehouse), a claims-based frailty index (as developed by Kim et al. (2018) to predict death, disability, recurrent falls, and health care utilization), age and sex.

Trial Participation Sample. The second cohort was developed to compare the SAE risk of trial participants to the full population of patients with the targeted disease, using the same SEER-Medicare data from 2014-2019. Since 2014, Medicare has required reporting of National Clinical Trial (NCT) database identifiers in claims for trial-related services. We use this reporting to identify trial participants in Medicare claims data, and link to the specific NCT record to identify the trial's eligibility group (National Library of Medicine, 2026). Prior research has validated the

[8]See Bishnoi et al. (2021); Bittoni et al. (2018); Du et al. (2005); Freedman et al. (2014); Gunturu et al. (2022); Hansen et al. (2014); Herbach et al. (2022); Hershman et al. (2013); Rashid et al. (2015); Reeder-Hayes et al. (2017); Sanoff et al. (2012); Wieder and Adam (2023).

use of these NCT records to identify participants in cancer trials (Green et al., 2022a). Following methods developed in Shah et al. (2025b), we used each trial's clinicaltrials.gov record to limit to randomized trials that tested a drug or biological agent. Then, we hired an oncologist who manually reviewed each trial with 5 or more SEER-Medicare participants; the physician identified the trial's enrollment criteria, including the targeted cancer subtype, stage, and treatment line. This review excluded trials that were not intended to treat the cancer (e.g., an RCT to prevent anemia) or were not specific to a single cancer (e.g., an RCT testing a drug that treats multiple types of solid tumors at once).

The Trial Participation Sample is used to make across-patient comparisons of the characteristics of trial participants and non-participants, and thus requires us to build a comparable sample of non-trial-participants who would potentially be eligible for the treatment tested in the trial. To support this analysis, we developed narrow subcohorts of patients that closely matched the target population specified in each trial's inclusion criteria. These subcohorts are defined by the primary cancer, relevant tumor markers, stage, and treatment line, e.g., second-line treatment of advanced-stage non-small cell lung cancer. These cohort definitions were developed with the guidance of an expert oncologist, based on clinically-relevant treatment categories. The patient's primary cancer, genetic tumor markers and stage at diagnosis are observed in SEER data. The treatment line is defined by how many prior treatment regimens the patient has had to date (so a second-line treatment is a treatment given only after a first therapeutic regimen failed), and we coded these based on observed drug treatment regimens in Medicare claims. In some cases, we also infer cancer stage has advanced beyond the stage at diagnosis based on the patient's treatment regimen.

For advanced stage cancers, we construct a target population of patients receiving active drug treatment. Because the drug treatments we leverage for cohort identification are specifically targeted to advanced cancers, this cohort captures both patients with advanced stage at diagnosis and those with disease progression to advanced stage. By contrast, there are multiple treatment strategies for early stage cancers, many of which do not use drug treatment. As a result, we construct a target population of patients who were diagnosed at an early stage regardless of treatment status. Given the differences in cohort construction, we report results for early vs. advanced stage cohorts

separately as a complement to our main, pooled analysis.

This detailed mapping of SEER-Medicare data to clinically-relevant treatment cohorts was not feasible for every disease state; we constructed 17 subcohorts spanning 4 common tumor sites (breast, lung, pancreatic and renal), and limit this analysis to these subcohorts. For more details on subcohort construction and definitions of the index date, see Appendix Table A8. For each patient in this cohort, we use 1-year claims history to measure the patient's comorbidities and frailty index, as well as sex and age.

3.2 Summary statistics

Summary statistics for the Adverse Event Sample are reported in Table 1, column 1. The average patient age is 74; 66% of patients are female; and 84% are White. Patients experience significant SAE risk after treatment initiation, with 10.35% of patients experiencing at least one hospitalization with primary diagnosis corresponding to an SAE within 90 days of treatment initiation. Appendix Table A9 further describes the frequency of each SAE category. The most common type of SAE is infection, comprising just over half of the total events. Chemotherapy can affect the immune system, increasing vulnerability to infection (e.g., pneumonia). The next most common categories are hematologic complications and kidney injury, affecting 2.2% and 1.7% of treated patients within 3 months; nephrotoxicity is another common side effect of cancer drugs.

Table 1 columns 2 and 3 report summary statistics for the trial participation cohort. Our sample includes 852 trial participants from 112 distinct trials. Rates of common comorbidities are lower among trial participants compared to non-participants. In Table 2, we show further evidence that trial participants are healthier than non-participants, after controlling for disease state fixed effects (i.e., cancer type $\times$ stage at diagnosis $\times$ treatment line). The estimates indicate that trial participants are less likely to have each of the 19 out of 20 measured comorbidities and have lower values of the Kim Frailty index (Kim et al., 2018). After Bonferroni correction for multiple comparisons, 16 out of 20 comorbidities have significantly lower incidence among trial participants at the 5% level. Trial participants are 3 years younger on average than non-participants (among our Medicare sample aged 65+). This evidence suggests that there is a selection pattern of healthier

patients for trial participation. In the analysis that follows, we will assess what these differences imply for the external validity of trial findings.

Appendix Table A10 provides further details on the trials included our analytic sample. 96% of the trials studied are Phase 2 and Phase 3 evaluations, which together form the crucial evidence base for FDA approval decisions. For cancer drugs, Phase 2 trials (43% of our sample) are designed to evaluate a new drug's effectiveness and monitor short-term safety outcomes (which would include the types of SAEs we study here). Phase 3 trials (54% of our sample) are larger trials that often compare new treatment against the current standard of care, and test for efficacy and adverse reactions. Our sample includes three Phase 1 trials, which are smaller trials that evaluate safe dosage ranges, and one Phase 4 trial that is conducted after FDA approval.

Appendix Table A11 reports that 62% of trials in our sample are industry-sponsored, and 15% of the trials are eventually cited in an FDA approval decision. Note that this rate likely understates the proportion of trials in our sample that were considered in FDA decisions or conducted with the intent of supporting an application to the FDA, since it only covers cases when a trial successfully supported an approval decision to date.[9]

Returning to the Adverse Event Sample, Figure 1 illustrates our identifying variation: this plot shows the average monthly SAE rate before and after cancer diagnosis. The plot separates patients into four groups based on the timing of treatment initiation: 3, 4, 5, or 6 months after diagnosis. In all four groups, SAE hospitalizations spike up initially around the month of cancer diagnosis. This pattern could occur because cancer itself causes worsening health and increases the hospitalization rate for a variety of health risks. The hospitalization rate falls in months 1 and 2 after diagnosis, but spikes up sharply in the month of drug treatment initiation. Each group reaches its peak SAE hospitalization rate in the month of treatment initiation. This graph illustrates why we exclude patients who initiate treatment within 2 months of diagnosis from our estimation sample: for these patients, it is difficult to disentangle the health event of cancer diagnosis from the effects of treatment initiation. It also shows that patients who initiate treatment in months 3–6 after diagnosis have similar hospitalization rates over the pre-period, bolstering confidence that these

[9]The FDA does not routinely release documentation of non-approval decisions, so it is difficult to link trials to unsuccessful applications.

groups are comparable and evolving on parallel trends.

4 SAE Treatment Effects

We start by describing how we construct SAE risk, identifying the attributes which predict adverse events among treated beneficiaries. Second, we relate adverse event risk to adverse event treatment effects within a difference-in-difference framework.

4.1 Estimating SAE Risk

Methods. We use a LASSO regression to predict the risk of SAEs following treatment initiation. The outcome variable for this analysis is the average of three monthly indicators for having any SAE hospitalization, calculated in the month of treatment initiation and two months following. We denote this outcome SAE_{ic} for the SAE rate of patient i with cancer type and stage c. Because this outcome requires three months of post-treatment follow-up, we exclude patients who initiated treatment after February 2020 (who would not have a complete three-month window before the end of our data in May 2020).

The estimating equation is as follows:

$$SAE_{ic} = \beta X_i + \phi_c + \varepsilon_i \text{ subject to } \Sigma|\beta_j| \leq t \tag{1}$$

The LASSO predictors X_i include indicator variables for 21 comorbidities, total comorbidity count, Kim frailty index (Kim et al., 2018), age (linear and quadratic terms), and sex. All comorbidities are measured at the time of cancer diagnosis (strictly prior to beginning any cancer treatment). The LASSO also includes fixed effects ϕ_c for 20 interactions of cancer type and stage at diagnosis; these control variables are not subjected to LASSO regularization.

We estimate this regression in 100-fold cross-validation, leaving out 1% of the sample at a time, to obtain a patient-specific prediction of SAE risk that is calculated from a sample that excludes the index patient. To construct a risk measure that predicts variation in SAE risk within a trial targeting a given cancer type, we exclude cancer type by stage variation from the predicted risk

index. Specifically, we compute: $Risk_i = \hat{\beta}_{-i} X_i + \overline{\phi}$ where $\overline{\phi}$ is a constant parameter that centers the predicted SAE rates around the overall mean SAE rate in the sample.

Results. Table 3 reports the results of our SAE risk prediction. To summarize the 100 separate hold-1%-out LASSO models, we report results from a single model estimated on the pooled data. The LASSO prediction retains 17 out of 21 comorbidities with nonzero coefficients, and also retains the total number of comorbidities, the Kim frailty index, age^2, and an indicator variable for whether the patient is female. The two most important predictors are the Kim frailty index and chronic kidney disease. A one standard deviation increase in either variable predicts a 0.5 percentage point increase in SAE risk, from a mean of 3.3% risk per month. Using the hold-one-out LASSO model to predict SAE risk for each patient ($Risk_i$), the resulting distribution indicates wide dispersion in risk across treated patients, with the 10th percentile patient having a 1.3% chance of an SAE each month, while the 90th percentile patient's risk is over 4 times larger at 6.2% per month.

4.2 Estimating SAE Treatment Effects

Methods. The variation in SAE risk estimated above could reflect both differences in treatment effects that depend on patient covariates and differences in baseline risk of hospitalizations for SAE conditions. In the second stage of analysis, we estimate the effect of treatment initiation on SAE hospitalizations and test whether these effects are larger among patients with higher SAE risk. We use two alternative methods for this analysis, drawing on recent two-stage approaches to event study analysis that address variation in treatment timing and possible treatment effect heterogeneity (Borusyak et al., 2024; Gardner, 2022). The main goal of this analysis is to estimate the change in the SAE hospitalization rate before vs. after treatment initiation.

Our analytic approach isolates comparisons of patients who recently initiated treatment (0, 1, or 2 months ago) to patients who are about to initiate treatment (1, 2, or 3 months in the future). Given that SAE rates increase around the time of cancer diagnosis (even in the absence of drug treatment), we control for months relative to cancer diagnosis in all of our regression analyses.

The first approach models SAE outcomes SAE_{igpt} for patient i who is in treatment group g, p

months since diagnosis in calendar month t as follows:

$$E(SAE_{igpt}) = \theta_0 Treat_{it} + \theta_1(Risk_i - \overline{Risk})Treat_{it} + \xi_g + \delta_p + \gamma_t + W'_{it}\beta \tag{2}$$

In equation 2, $Treat_{it}$ is a binary variable indicating that patient i received cancer drug treatment in month t. θ_0 is the average effect of treatment, and θ_1 allows the treatment effects to vary with each patient's SAE risk (calculated as a function of their comorbidities, frailty, and demographics at the time of cancer diagnosis, as described above). ξ_g captures treatment group fixed effects: treatment groups are defined by the number of months since diagnosis when the patient initiates treatment. (In our SAE sample there are four treatment groups, corresponding to treatment initiation dates 3, 4, 5, and 6 months after diagnosis.) δ_p captures health evolution before and after diagnosis, by including fixed effects for each month before and after diagnosis (from -12 to +6). γ_t captures calendar time fixed effects to control for time trends and seasonality. Finally, W'_{it} includes patient characteristics, including cancer type by stage fixed effects, patient age, and predicted SAE risk.

We estimate this equation in two stages, using an imputation estimator adapted from Borusyak et al. (2024).

1. We restrict the sample to untreated observations only. Because all observations in our sample are treated within 6 months after cancer diagnosis, this restriction limits to patients who are not-yet-treated. Within the not-yet-treated sample, we estimate:

$$Y_{igpt} = \xi_g + \delta_p + \gamma_t + W'_{it}\beta + \varepsilon_{igpt} \tag{3}$$

2. For each treated observation in months 0, 1 or 2 after treatment initiation, we use our estimated coefficients from step 1 to impute SAE outcomes in the post-period in the absence of treatment. We then subtract imputed outcomes (assuming no treatment) from observed outcomes (for treated individuals). Specifically, we calculate:

$$\hat{\theta}_{igpt} = Y_{igpt} - \hat{\xi}_g - \hat{\delta}_p - \hat{\gamma}_t - W'_{it}\hat{\beta} \tag{4}$$

Our aggregate treatment effect estimate is a simple average of these $\hat{\theta}_{igpt}$. To test for heterogeneity in treatment effects for patients with different predicted SAE risk, we estimate the following regression:

$$\hat{\theta}_{igpt} = \theta_0 + \theta_1(Risk_i - \overline{Risk}) + \varepsilon_{igpt}. \tag{5}$$

Recall that $Risk_i$ is predicted as a function of the patient's comorbidities, frailty, and demographics, using the coefficients from a LASSO model estimated in a sample that excluded the index observation.

For all results estimating SAE effects, confidence intervals are calculated by a generalized method of moments following Gardner (2022), clustered at the patient level.

We also estimated an extended version of this regression model that allows us to plot event study coefficients before and after treatment initiation. To do so, we modify the first stage of the estimation procedure as follows. Using only untreated observations (from periods prior to treatment), we estimate the following equation:

$$Y_{gpit} = R'_{it}\theta^R + \xi_g + \delta_p + \gamma_t + W'_{it}\beta + \varepsilon_{igpt} \tag{6}$$

where R'_{it} includes a vector of fixed effects for months -6 through -1 prior to treatment initiation and θ^R captures the effect of being R months from treatment initiation. We use months more than 6 months prior to treatment initiation as the reference period. To estimate post-period coefficients, we average the estimates $\hat{\theta}_{igpt}$ from Step 2 within each post-treatment month (0, 1 or 2).

Results. Figure 2 displays the results of the event study framework. The pre-period shows no statistically significant effects, bolstering the parallel trends assumption for SAE risk in early- and later-treated groups. SAE risk increases in the month of treatment initiation and the 2 months immediately afterwards, by 2 to 3 percentage points per month. Note that we can only identify 3 months of post-treatment initiation effects in our current sample, which limits to patients who initiated treatment within 3-6 months from diagnosis.[10] The descriptive evidence plotted in Figure 1

[10]By month 6, all patients have initiated treatment, so we do not have a not-yet-treated group to identify time-since-diagnosis effects for month 6. This means the longest treatment horizon for which we can estimate a treatment effect is 2 months post-treatment initiation, which takes place 5 months from diagnosis for the month 3 treatment

suggests that this 3-month post-period covers the months with peak SAE risk.

Table 4 summarizes our difference-in-differences findings, and formally tests whether our measure of SAE risk is predictive of heterogeneity in the impact of initiating cancer drug treatment. Column 1 reports estimates from our baseline specification that controls for calendar time, time since diagnosis, SAE risk, age, cancer type X stage, and fixed effects for cohorts defined by the timing of treatment initiation. On average, over the three calendar months following treatment initiation, the risk of SAE increases by 2.4 percentage points (95% CI: 2.1 to 2.7 p.p.) from a pre-treatment baseline of 0.96 percentage points, representing a 250% increase.

Table 4 Column 2 reports estimates where we test for heterogeneity in SAE treatment effects, depending on patients' predicted SAE risk (as estimated by the jackknifed LASSO model). We find that patients whose comorbidities, frailty, age and sex predict higher SAE risk also experience larger increases in SAE hospitalizations after treatment initiation: roughly half of the observed variation in SAE risk translates into differences in SAE treatment effects. This pattern is consistent with the possibility that treatment effects are proportional to baseline risk, so that about half of the SAEs among treated patients reflect treatment effects causally induced by the cancer drugs and half of the adverse events may have occurred in the absence of treatment. Patients with 1 standard deviation greater SAE risk experience a 0.8 p.p. greater increase in SAE rate upon treatment initiation (standard error: 0.1 p.p.), which is an increase of one-third over the mean SAE treatment effect of 2.4 p.p. per month.

Table 4 columns 3 and 4 assess the robustness of our SAE findings to an alternative specification that includes patient-level fixed effects. The baseline specification and this alternative yield remarkably similar estimates of both the average treatment effect and treatment effect heterogeneity as a function of patients' SAE risk.

Figure 3a displays a binned scatterplot showing the relationship between SAE risk and patients' estimated individual treatment effect. The scatterplot shows a strong relationship, with higher SAE risk corresponding to larger increases in SAE rates after treatment initiation. Taken together, these results imply that cancer drugs substantially increase patients' likelihood of hospitalization for a

initiation group.

potential SAE, and these risks vary systematically and predictably across patients.

Robustness. We assess the robustness of these results to several alternative specifications, varying the functional form of the estimation equation, risk model, and coding of patient deaths.

For a risk model to be applicable in prospective regulation of drug development, it needs to generalize beyond the specific drug or disease context that was used to estimate the algorithm. To assess the generalizability of our approach, we consider two alternative ways of estimating the risk model. First, we estimate seven versions of our LASSO risk model, holding out each of the seven major tumor sites included in our analysis. Then we apply the risk model estimated in the sample that excludes the index patient's cancer type to predict the patient's SAE risk in our event-study framework. Results reported Table A12 demonstrate similar coefficients to our baseline analysis; a patient with 1 SD higher SAE risk has a 0.7 p.p. (standard error: 0.1 p.p.) higher monthly likelihood of an SAE when we use the hold-out-cancer risk model, compared to 0.8 p.p (SE: 0.1 p.p.) higher with the baseline risk model. Second, we estimate the LASSO risk model excluding any patient who had any prescribed cancer drug that overlaps with a drug taken by the index patient within 3 months of treatment initiation. The coefficient attenuates slightly but remains significant and is not statistically distinguishable from the baseline estimate; a patient with 1 SD higher SAE risk has a 0.6 p.p. (SE: 0.1 p.p.) higher monthly likelihood of an SAE in the hold-out drugs analysis. These hold-out cancer and hold-out all drugs results are conservative, because many new drugs are tested for existing cancers and many new drugs are tested in combination with existing therapies; thus, even Phase 2 and 3 clinical trials often have same-cancer and overlapping-drug predicates that could inform risk models.

Appendix Figure A2 and Appendix Table A13 report results from an alternative sample, expanded to include patients who initiate drug treatment between 3-11 months after diagnosis (rather than 3-6 months, as in our baseline sample). Results are extremely similar across both samples, although the broader sample shows small but statistically significant pre-trends in the two months preceding treatment initiation. We interpret this as evidence that patients who initiate treatment much later after diagnosis may have a different evolution in their baseline SAE risk, and thus we prefer comparing patients whose treatment initiation dates are relatively close together (as in the

baseline sample). An advantage of the broader sample is that it allows us to estimate additional post-period effects. We find that SAE rates trend down beginning 3 months after treatment initiation, although treatment discontinuation (often spurred by adverse events) may contribute to this downward trend.

Appendix Table A14 provides suggestive evidence on the external validity of our findings to patients with earlier treatment initiation dates, between months 0-2 following diagnosis. Using our model of SAE risk (reported in Table 3, we predicted SAE risk for each subcohort defined by the month of treatment initiation (relative to diagnosis). We do not find a strong relationship between the timing of treatment initiation and predicted SAE risk, with average monthly risk ranging from 3.4 to 4.1%. This suggests that our sample of patients who initiate treatment between 3–6 months after diagnosis may have similar SAE risk to earlier treated groups.

Finally, we test an alternative approach to handling patient deaths. Our baseline analysis includes data for 3 months post-treatment for all patients; if a patient dies after treatment initiation but before 3 months have elapsed, we record their SAEs in subsequent months as zeros. In Figure A1, we show results from an alternative specification where we censor observations from months following the patient's death. This alternative specification generates similar, though slightly larger treatment effect estimates in months 1 and 2 following treatment initiation.

5 SAEs and Trial Participation

5.1 Econometric approach

The second phase of analysis investigates the relationship between SAE risk and trial participation. Recall that the Trial Participation Sample is limited to specific subgroups that we can match precisely to trial target populations, based on the criteria outlined in detail in Appendix Table A8. We use the SAE risk prediction model constructed in the SAE Sample to predict patient-level SAE risk in the Trial Participation Sample. To transport the SAE risk prediction model to the Trial Participation sample, we use patient-level risk factors and coefficients recovered from our LASSO regression described above: $Risk_i = \hat{\beta} X_i + \overline{\phi}$. Because we do not observe the average SAE rate in

the Trial Participation Sample, we center these predictions around the mean SAE rate in the SAE sample.[11]

Next, we test whether our measure of SAE risk predicts differences in trial enrollment probability, conditional on the patient's disease state (cancer type, tumor markers, disease stage, and treatment line). We estimate logistic regressions to allow SAE risk to have a proportional effect on the odds of trial participation::

$$\log\left(\frac{Pr(Trial_{is}=1)}{1-Pr(Trial_{is}=1)}\right) = \alpha Risk_i + \phi_s + \varepsilon_i. \tag{7}$$

The main coefficient of interest is α, which captures the relationship between patient-level SAE risk and the log odds of trial participation. We control for disease state fixed effects ϕ_s where disease state references the subcohorts defined by cancer type, stage, genetic markers, and treatment line (as summarized in Appendix Table A8). In some specifications we also control for patient-level demographic characteristics: age (linear and quadratic terms), sex, race, and ethnicity.

Finally, we compare the distribution of SAE risk across trial participants and non-participants. To ensure differences between the two cohorts are not driven by variation in the trial participation rate across disease states, we reweight each observation in the full population (which includes both participants and non-participants) to match the disease-state distribution among the restricted sample of trial participants only (Barsky et al., 2002; Chandra et al., 2024). Specifically, if s indexes disease state cohorts, then we reweight each observation by:

$$w_s = \frac{P(DiseaseState = s|Trial = 1)}{P(DiseaseState = s)}. \tag{8}$$

After reweighting, we construct kernel density plots comparing the distribution of SAE risk in the full population to risk among trial participants, and we also compare the average SAE risk. Finally, to assess the implications of these differences in SAE risk for reported SAE treatment effects, we use the estimates from Equation 5 to construct predictions of SAE treatment effects for each patient

[11] Recall that the Trial Participation Sample includes some early stage cancer patients who are not currently treated with cancer drugs, and as a result do not experience drug-induced SAEs. We use this choice for these early stage cohorts because there are no widely accepted drug treatment options for these early stage cancers currently.

(given their SAE risk $Risk_i$): $\hat{\theta}_i = \hat{\theta}_0 + \hat{\theta}_1(Risk_i - \overline{Risk})$. We compare the average SAE treatment effect among trial participants versus among all patients (in the reweighted sample).

5.2 Results: SAE Risk and Trial Participation

Figure 3b shows a binned scatterplot of the relationship between trial participation and SAE risk, controlling for fixed effects for each disease state. There is a strong, downward-sloping relationship between trial participation and SAE risk, over the whole range of observed SAE risk. Table 5 column 1 reports the results from a logistic regression of trial participation on SAE risk, controlling for disease state fixed effects. As reported in Panel A, a 1 standard deviation increase in SAE risk (a 1.8 percentage point change) reduces the odds of trial participation by 40.7% (standard error: 2.5); this relationship is statistically significant at the 1% level. To further contextualize the magnitude, consider that a patient at the 10th percentile of the SAE risk distribution would have a 1.36 percentage point increase in their monthly risk of an SAE upon initiating a cancer drug and a 0.8% rate of trial participation (see Appendix Table A15). By contrast, a patient at the 90th percentile of the risk distribution has SAE treatment effects that are over 2.5 times larger (3.6 percentage points per month), yet has a 4 times smaller chance of trial participation (0.2%).

Next, we split our trial participation cohort into two subgroups: advanced stage cancers and early stage cancers. When constructing the target population for advanced stage cancers, we require that patients be receiving a cancer drug therapy that is specifically indicated for this disease stage.[12] This ensures that all patients in the comparator population are being actively treated—the sample will necessarily exclude patients for whom treatment is not consistent with their goals of care or for whom physicians judge that treatment would offer no clinical benefit due to the patient's frailty or disease state. Table 5 column 2 reports a coefficient in the advanced stage subgroup similar in magnitude to that reported in column 1 for the pooled sample. A 1 SD increase in SAE risk is associated with a 38.2% lower odds of trial participation (standard error: 3.6) among patients with advanced stage cancer. Thus, selective trial enrollment cannot be explained by selection into

[12] We do this in part because while our data identifies cancer stage at diagnosis, we cannot directly observe disease progression after diagnosis. Thus, we follow the advice of oncologist experts and identify patients with advanced disease stages by their use of treatment with drugs that are specifically used for advanced cancers.

drug treatment: trial participants have systematically lower SAE risk than patients receiving active treatment for the same disease.

Table 5 column 3 reports results for patients with early stage cancers; this cohort does not limit to patients who currently receive cancer drugs, because the standard of care for many of these early stage cancers do not require treatment with drugs. (Early stage cancers are commonly treated with surgical resection and/or radiation.) As a result, clinical trials targeting this population aim to introduce drug treatment to a population who may not currently receive drugs. We cannot know for certain which patients among this early-stage cohort might receive a new drug, so we include all patients with the relevant cancer type, tumor markers, and stage in our analysis. We continue to find a strong, negative relationship between SAE risk and trial participation, of similar magnitude. A 1 SD increase in SAE risk is associated with a 41.5% lower likelihood of trial participation (standard error: 3.5).

We also assess the relationship between SAE risk and trial participation conditional on patient demographics. The FDA has focused attention on improving trial generalizability by ensuring that trial enrollees match the age, sex, and race distribution of the target population (FDA 2022, 2014). Would improving the demographic representativeness of trial enrollees be sufficient to close the estimated gaps in SAE effects? Table 5 Panel B reveals that controlling for sex, race, and age (with linear and quadratic terms) does little to change the estimated relationship between SAE risk and trial participation. The pooled sample coefficient attenuates only slightly with the addition of these control variables, from a baseline estimate of -28.3 to a controlled estimate of -22.9; despite the attenuation, the coefficient remains highly statistically significant. This finding suggests that improving demographic representation of clinical trials is insufficient for ensuring that SAE treatment effects generalize. Most of the selection of lower-risk patients into trial enrollment occurs within demographic groups.

Appendix Table A16 repeats this analysis using a linear (rather than logistic) regression. For the linear regression, the outcome variable is $1\{TrialParticipant\}/Pr(TrialParticipant|DiseaseState)$, so that the probability of trial participation is rescaled across disease states to account for disease-specific variation in trial enrollment rates. We find similar magnitude results with this specification.

In column 1, a 1 SD increase in SAE risk would reduce the likelihood of trial participation by 42% ($= .018 * -22.887$).

Finally, Appendix Table A17 investigates whether similar patterns of selection into trial participation arise when we restrict our attention to industry-funded, Phase 3 trials. These trials are the typically the pivotal trials on which FDA decisions are based, and they represent a plurality of trials in our data (see Appendix Tables A10 and A11). Results are very similar to the pooled analysis reported above; with nearly identical magnitude, and even less attenuation of the coefficient after controlling for age, sex, and race.

5.3 Implications for Estimating SAE Treatment Effects in Trials

We consider the implications of our findings for the average SAE risk reported in trials. Figure 4a shows kernel density plots of the distribution of SAE risk among all patients in our cohort, and among trial participants. The distribution of SAE risk for trial enrollees has a lower mode and less variation compared to matched cohort of non-enrollees. The average SAE risk for trial participants is 3.1%, compared to a risk of 3.8% among all patients; the difference is statistically significant at the 1% level. Using the relationship between SAE risk and SAE treatment effects estimated in Section 4.2, this difference corresponds to an average SAE treatment effect of 2.4 percentage points for trial participants compared to an average SAE treatment effect of 2.8 percentage points for the full population, a 14% difference (95% confidence interval: 10% to 18%).[13]

Our sample is limited to patients who met the age eligibility criterion for Medicare for at least 1 year prior to cancer diagnosis, and are thus at least 66 years old. Our findings suggest that subgroup analyses of patients over 65 are likely to understate true SAE treatment effects. The true gap between SAE treatment effect for trial enrollees and the target population is likely greater, since patients over 65 years old are underrepresented in clinical trials (Varma et al., 2023). Because older patients are more likely to be frail and have multiple comorbidities, SAE treatment effects likely increase with age. Thus, underrepresentation of patients over 65 in trials would further widen

[13]The variance of the proportional treatment effect difference was computed by the delta method. The variance combines the covariance matrix for the mean treatment effect and risk coefficient (from the SAE analysis) with variance estimates of the trial-participant and reweighted target population mean SAE risks. The reported total SE is the square root of the sum of these two variance components.

the gap between trial participants and the target population.

In Figure 4b, we further explore whether industry-sponsored trials have different patterns of selection compared to investigator-initiated trials. Consistent with the possibility that industry-sponsored trials have stronger incentives to reduce SAE among trial participants, we find that industry-sponsored trials are less likely to draw participants with above-average SAE risk. However, the difference in mean SAE risk across industry-sponsored vs. non-industry sponsored trials is modest and not statistically significant: 3.1 vs. 3.3 percentage points per month. It is worth noting that even among trials initiated by an academic investigator, many report funding from pharmaceutical companies; thus, industry preferences may influence aspects of trial design for both types of trials analyzed here.

Although there are not significant differences in trial selection related to the sponsor, there could nevertheless be variation across trials in the extent of selection on SAE risk. To investigate, we estimated a random effects maximum likelihood model, which allows for trial-level heterogeneity in the difference between mean SAE risk in the trial vs. the relevant target population. Weighting each trial equally, trial participants have a 0.85 percentage point lower monthly rate of SAEs. The raw standard deviation across trials is 0.68 percentage points. After adjusting for sampling error (due to limited number of participants in each trial), we estimate the true cross-trial standard deviation at 0.49 percentage points [95% confidence interval: 0.36 to 0.59 percentage points]. This suggests that trials differ meaningfully in the extent to which they select on SAE risk, raising the possibility that changes to trial enrollment procedures (e.g. trial site selection or exclusion criteria) could achieve more representative enrollment.

Selective enrollment into trials may occur for two reasons. First, trials may enroll at sites that treat patients who are healthier on average and less likely to suffer SAE. Second, within trial-enrolling sites, healthier patients may be more likely to enroll in trials either due to patient preference, physician views on suitability, or trial exclusion criteria. We now consider the potential role of trial siting, by examining the distribution of SAE risk at trial-enrolling sites compared to among trial enrollees and among the full population. We identify patients whose attributed oncology practice enrolls patients in clinical trials following methodology previously developed in

Shah et al. (2025a), and reweight patients at trial-enrolling sites to match the joint distribution of disease states and attributed oncology practices among trial enrollees. Appendix Figure A3 reports our findings. Patients at trial-enrolling sites have significantly *lower* SAE risk than the full population but significantly *higher* adverse event risk than trial enrollees. Site selection can explain only 24% of the difference between the average SAE risk of the trial enrollees vs. the full population.[14]

Finally, we find that clinical trials enrollment would need to be twice as large to conduct adequately powered subgroup analyses of SAE treatment effects in high-risk groups under current enrollment patterns compared to representative enrollment. We conducted power calculations to find the trial size needed to detect a treatment effect on SAE outcomes among a high-risk subgroup, with 80% power at the 5% significance level. The high-risk group is defined as the top 30% of SAE risk distribution in our trial participation cohort; monthly average SAE risk is 6.1% in this group, which is 60% larger than the overall mean. We assume a three-month trial duration and monthly SAE treatment effect as estimated in Table 4 Column 2. Under current trial enrollment patterns, only 15% of trial enrollees are in the top 30% of the risk distribution, and a trial would need to enroll 2273 total participants to have the 350 high-risk participants needed to power subgroup analyses. If enrollment were proportional to the population, then a trial would need to enroll half as many participants (1133) in order to have 350 high-risk participants needed to power subgroup analyses.

6 Regulating SAE Representativeness

A welfare-maximizing regulator would maximize the expected quality of approval decisions, balancing recruitment costs, statistical power, and external validity of both benefits and harms. We do not solve that full design problem here. In particular, we do not analyze the recruitment cost of representative trials or the effects of representativeness regulation on which drugs get developed and for whom (Kao and Oostrom, 2024; Michelman and Msall, 2024), all of which are inputs to

[14] Calculation based on the reweighted means of the three distributions: $.24 = (.0342 - .0353)/(.0307 - .0353)$, within the sample with non-missing practice attribution.

optimal policy. Instead, we study an incomplete but monitorable dimension of external validity: predicted bias in SAE risk. We first lay out a formal framework for measuring trial representativeness (Section 6.1), then use it to address the concern that regulating SAE representativeness alone could worsen net-benefit representativeness, and propose a regulatory framework in which sponsors quantify SAE bias ex ante and either reduce it or justify any residual bias. Finally, we perform some back of the envelope calculations to quantify the potential benefits of the regulation we propose.

6.1 A formal framework for trial representativeness

Let $\tau_1, \ldots, \tau_N$ denote net impacts of treatment in subgroups $j = 1, \ldots, N$ which comprise respectively fractions $p_1, \ldots, p_N$ of the total population who will be treated with a drug (should it be approved). Since trials are not typically powered for subgroup analysis, doctors learn only the estimated average treatment effect from trials (Alosh et al., 2015). Let r_j denote the fraction of each group j in a given trial. A simple model of trial design would imply that trialists seek to minimize the mean-squared error between $\hat{\tau}_{ATE}$ estimated from a trial and $\tau_{ATE} = \sum_j p_j \tau_j$, the true average treatment effect in the population. Classic results imply that, if trials are sufficiently large or all groups have equal variance of treatment effects, the mean-squared error minimizing trial design would represent all groups proportionately (Neyman, 1934; Cochran, 1977), setting $r_j = p_j$.[15]

In practice, trials are conducted via convenience sampling, and so $r_j \neq p_j$. Participants are recruited from a relatively small set of (non-randomly selected) trial sites, with physicians exercising discretion to make enrollment offers and patients endogenously choosing whether to participate. Because randomization occurs after this enrollment process is completed, trials have strong internal validity. But trials' external validity relies on how representative treatment effects are for trial participants relative to the target population, given that participants are not a simple random sample of the target population.

Suppose that the net impacts of a drug for patient subgroup j can be written as $\tau_j = \alpha_j + \delta\gamma_j$, where α_j denotes treatment effects for intended medical benefits and γ_j denotes treatment effects

[15] More generally, the optimal allocation may deviate from proportionality when the variance of treatment effects varies across groups.

for harms (i.e., adverse events), which have a relative welfare weight $\delta > 0$. We normalize the signs of each component so that α_j is negative when the patient receives beneficial effects of treatment (e.g., through reduced probability of mortality), and γ_j is positive when patients experience harms of treatment (e.g., through increased risk of organ failure).

We define $B_\gamma = \sum_j (r_j - p_j)\gamma_j$ as the bias with respect to severe adverse events—estimating this object was the focus of much of the empirical analysis above. A proportional trial could obtain unbiased estimates of harms $E(\gamma_j)$ and benefits $E(\alpha_j)$ separately. Lack of proportionality with respect to γ_j (i.e., $B_\gamma \neq 0$) is thus diagnostic that a trial is not setting $r_j = p_j$. However, one could conduct a similar test using any observable characteristic. Our question here is, "Why do we care about representativeness with respect to γ_j specifically, rather than any other arbitrary patient characteristic (e.g., people with last names starting with K)?"

We provide two justifications. A first answer is that doctors, patients, and regulators may care about average harm $E_p(\gamma_j)$ in its own right separately from average net benefit $E_p(\tau_j)$ (where the p subscript denotes population expectations). As we discussed in Section 2 above, if a cancer treatment is likely to prolong life expectancy on average but raises the risk of a debilitating stroke, patients want to be informed about the latter risk. We may thus want to design trials that are representative in terms of γ_j.

A second answer is that, even if doctors or regulators care only about net impacts τ_j, trials which are less biased in terms of average harm $\overline{\gamma}$ will also tend to be less biased in terms of average net impacts $\overline{\tau} = E_p(\tau)$, under conditions we make precise. Setting $r_j = p_j$ (i.e., trial is a random sample of the population) would lead to unbiasedness of both harms and net impacts, but there are other ways of oversampling some groups and undersampling others to get unbiasedness in terms of harms $\overline{\gamma}$ but not net impacts $\overline{\tau}$. Below, we derive conditions under which trialists seeking representativeness in terms of severe adverse events in the least costly possible way will also improve net impacts.

6.2 Does Improving SAE Representativeness Improve Welfare?

Because our empirical results focus on the harm side, a natural concern is that harms and benefits may be correlated across patient subgroups in a way that leads regulation of harms alone to backfire. Suppose that high risk, high benefit patients are sometimes excluded from the trial because they are expensive to enroll, despite potentially making the drug look even better in the trial results. Additionally, suppose that despite this, status quo trials still overstate drug benefits by disproportionately excluding high-risk, low benefit patients. In this case, forcing trials to enroll a representative share of high-SAE-risk patients could *worsen* how much trials overstate benefits, if marginal high-risk patients have especially large benefits relative to the typical patient taking the drug.

In Appendix A2, we formalize this idea by assuming that trial sponsors seeking unbiasedness in terms of γ (severe adverse events) will shift the underlying shares of enrollees from each subgroup in the way that achieves unbiasedness while changing the Euclidean distance between the shares as little as possible.[16] Recall that net benefits are denoted by $\tau = \alpha + \delta\gamma$, and define $B_\alpha = \sum_j (r_j - p_j)\alpha_j$ (the initial bias in medical benefits α) and $B_\gamma = \sum_j (r_j - p_j)\gamma_j$ (the initial bias in severe adverse events γ). Define $h = \frac{Cov_p(\alpha,\gamma)}{Var_p(\gamma)}$, the population regression weighted coefficient of α (benefits) on γ (harms). The Appendix develops the more general case, but we focus here on the case we find empirically most relevant in our calibration below: (1) both B_α and B_γ have the same sign, so trials understate SAE risk ($B_\gamma < 0$) and overstate medical benefits ($B_\alpha < 0$) (e.g., to maximize chances of FDA approval) and (2) $h < 0$, meaning that patients who have more induced SAEs ($\gamma > 0$) tend to have larger benefits from treatment ($\alpha < 0$).

In this case (or $B_\alpha = 0$), changing trial enrollment patterns to achieve γ unbiasedness will reduce τ bias when:

$$-h \leq \delta \tag{9}$$

where $\delta > 0$ is the relative welfare weight attached to SAEs relative to medical benefits (a positive

[16] Shifting shares in this way would require trial sponsors to know r_j and p_j before conducting trials. In the appendix, we assume that in trial k, net impacts are given by $\tau_{j,k} = \beta_k(\alpha_j + \delta\gamma_j)$. Trialists can then know $E(\beta_k)\alpha_j$ and $E(\beta_k)\gamma_j$ for each subgroup from pooling evidence from previous trials (as we do in our empirical work above) while still requiring a trial to estimate τ_j because of the β_k term.

ratio, e.g., the relative utility of a 1 pp reduction in infections compared to a 1 pp reduction in mortality). In other words, when patients with more induced harms also have larger benefits, the condition requires that this negative correlation not be so large that pushing trials to enroll more high SAE risk patients worsens representativeness on medical benefits by enough to outweigh the gains in SAE representativeness.[17]

Calibration. We conduct a calibration exercise to assess whether the condition in Equation 9 is likely to hold in practice in the context of cancer drug trials. Details of this exercise are available in Appendix A3, and Appendix Table A18 reports the calibration inputs and sensitivity checks. We summarize the exercise here. To estimate h, the relationship between heterogeneous harms and benefits of treatment, we first estimate medical benefits by combining estimates of cancer mortality risk with estimates of the average mortality risk reduction from treatment (20%). Next, using these measures of treatment benefits and our existing estimates of SAE harms, we regress α on γ. We find that $h = -0.049$, suggesting only a weak relationship between SAE treatment harms and treatment benefits, whereby patients with a 10 percentage point (p.p.) greater probability of a drug-induced SAE event would experience a 0.5 p.p. greater decline in 1-year cancer mortality from treatment.

In our empirical work above, we presented evidence that B_γ is negative, i.e., trials understate the risk of drug-induced harms. We do not have direct evidence about the sign of B_α, but we suspect it is likely negative or zero if trials select patients who are likely to have greater benefits (consistent

[17] To see how this condition might fail, consider a trial of an immune checkpoint inhibitor for metastatic non-small-cell lung cancer. PD-1/PD-L1 inhibitors can improve survival for patients whose tumors express biomarkers associated with immune response, such as high PD-L1 expression (Reck et al., 2016), but the same immune activation that makes these drugs effective can also produce immune-related serious adverse events across multiple organ systems (Postow et al., 2018). Suppose the original trial under-enrolls patients at high risk of severe immune-related toxicity, so $B_\gamma < 0$, while also over-enrolling patients likely to show a large antitumor response, so $B_\alpha < 0$. This could occur, for example, if the trial enrolls patients with strong performance status, intact immune function, and biomarker-positive tumors, while excluding patients with preexisting autoimmune disease or chronic immunosuppression, who are often excluded from checkpoint-inhibitor trials because of toxicity concerns (Khan et al., 2016). If, in the target population, greater baseline immune activation or preserved T-cell responsiveness raises both the probability of immune-related toxicity and the probability of antitumor response (Fan et al., 2021; Socinski et al., 2023), then $h < 0$: the patients added to make SAE risk more representative will tend also to have larger treatment benefits, i.e., more negative α. In that case, SAE regulation improves representativeness of harms but can worsen representativeness of benefits. If the additional treatment benefit associated with moving toward high-SAE-risk patients is large relative to the welfare weight placed on the additional serious adverse events, the trial's estimate of net impacts can become less representative even though its estimate of SAE risk becomes more representative.

with trial sponsors' incentives to demonstrate that the drug is effective). Given that $h < 0$, if $B_\alpha \leq 0$, then comparing $-h = 0.049$ to δ is sufficient for checking the condition in Equation 9. The δ parameter has only been previously estimated given hypothetical preference elicitation surveys, but we find that the existing estimates of the utility cost of an SAE are roughly 4 times larger than would be required for the condition in equation 9 to hold, meaning that regulating SAE representativeness alone is likely to improve net benefit representativeness for cancer drugs.

Clinical evidence on the harm-benefit correlation. As an alternative to this calibration exercise, we also look to the clinical literature to consider the possible correlation between treatment harms and benefits for cancer drugs. There is a significant selection bias challenge (sometimes called "immortal time bias" or "guarantee time bias") to understanding the relationship between treatment toxicity and treatment benefits: patients who have longer progression-free survival have the opportunity to experience longer treatment duration, and thus more time to experience potential adverse events (Giobbie-Hurder et al., 2013). Recent papers use various approaches to account for this form of bias (e.g., time-dependent Cox model, landmark analysis, inverse probability weighting), but these approaches still rest on a strong assumption of no unmeasured time-varying confounding. Thus, we interpret the evidence with caution. A meta-analysis of studies on cancer immunotherapy treatments found no relationship between SAEs and treatment efficacy (Fan et al., 2021).[18] There is some evidence that chemotherapy-induced neutropenias (a hematologic complication of treatment) are predictive of survival outcomes (Kasi and Grothey, 2018), but the relationship between neutropenia (defined based on laboratory testing of blood) and the hospitalization-based SAEs studied here is unclear. Other research has found that chemotherapy-related toxic effects are associated with long-run *declines* in quality of life, physical functioning, and survival, among older patients with frailty Baltussen et al. (2023); Schuurhuizen et al. (2018).

Taken together, both the formal calibration and the clinical evidence suggest that severe adverse events and treatment efficacy are at most weakly correlated for cancer drugs. The calibration

[18] Fan et al. (2021) did find that patients experiencing mild adverse events were more likely to benefit from treatment, but these were Grade 1 and 2 events that (by definition) do not require hospitalization. Our analysis in this paper restricts to adverse events that were the primary diagnosis on an inpatient hospital stay, and thus excludes Grade 1 and 2 events (U.S. Department of Health & Human Services, 2017).

condition in Equation 9 is satisfied with a substantial margin, indicating that improving SAE representativeness is likely to improve net-benefit representativeness as well, in our context. This motivates the regulatory framework we propose next.

6.3 A Proposed Regulatory Framework

In oncology, SAE representativeness is attractive as a regulatory target because severe harms matter directly to patients and regulators, and reducing SAE bias is likely to improve representativeness of net impacts (as shown above). While minimizing SAE bias should not be the sole design objective in trials, we argue that SAE representativeness is a monitorable guardrail that would complement existing regulatory requirements. We propose one potential approach to regulating SAE representativeness that requires more representative sampling, and then compare it to an alternative regulation based on reweighting with status quo enrollment patterns in simulations.

Concretely, we propose a framework consisting of five parts:

1. Trialists identify the target population should the drug be approved.
2. Trialists compute means of observable covariates in the target population and in the proposed trial population, denoted by $\bar{X}^{target}$ and $\bar{X}^{trial}$.
3. Given these means, use the LASSO model from Equation 1 and the scaling coefficient $\hat{\theta}_1$ from Equation 5 to compute $B_\gamma = \hat{\theta}_1(\bar{X}^{target} - \bar{X}^{trial})'\hat{\beta}$, the estimated SAE bias. If that bias is material, sponsors should either reduce it or justify the remaining bias in light of power, feasibility, recruitment costs, ethical constraints, or a prespecified transportability analysis.
4. When submitting trial findings for FDA review, report the target population definition, predicted SAE risk in the target population, and predicted SAE risk among enrolled patients.
5. In postmarketing surveillance, confirm alignment between predicted target population and realized target population. Misalignment could be directly penalized by the regulator, or could be used to identify cases where investment in post-market safety trials may be needed.

Alternative regulatory approaches could target the same external-validity problem at different points in the trial design process. Following the biostatistics literature on transportability, one

alternative is to leave enrollment unchanged but require sponsors to report reweighted trial analyses that transport trial estimates to the target population by matching the distribution of predicted SAE risk. On the one hand, the reweighting approach is attractive because it does not require changes in trial recruitment practice. Trialists would be required to collect additional data on patient comorbidities (to construct the risk index), and then calculate reweighted estimates of SAE harms and treatment benefits. The main drawback of this approach is that it offers substantially worse power because current trials contain few patients in high-risk strata; the approach may also be infeasible in cases where there is no overlapping support.

Appendix A4 describes a simulation exercise that compares this reweighting approach to our proposed regulation, benchmarking against current enrollment patterns. We simulated 1000 trials per disease state, with 500 participants per trial for each of 4 disease states with adequate data. For the purposes of the simulation, we assume SAE treatment effects vary with SAE risk consistent without our prior estimates. Across these simulations, our suggested regulatory approach has power to reject a null of no SAE treatment effect 79% of the time, compared to 60% power for the reweighting approach. Both approaches are nearly unbiased, under the assumption that our SAE risk model appropriately captures heterogeneity in SAE treatment effects. As expected, status quo enrollment has substantial bias and slightly lower power than our preferred regulatory approach.

Both regulatory frameworks described above reference the specific SAE risk model we develop here, which would be appropriate for oncology drugs. Adapting the framework to other disease targets would require developing an appropriate SAE risk model for those populations. Our work on cancer drugs suggests a blueprint for this future extension to other settings.

A natural concern is that the relevant target population is endogenous and evolves over time. Berger et al. (2021) document that the population treated with an approved drug frequently expands well beyond the trial-enrolled population through formal label expansions and off-label use, a dynamic that is particularly pronounced in oncology. Our framework operates within the existing FDA approval cycle: the relevant target population at each approval is the labeled indication, and subsequent label expansions are themselves submitted for FDA review, at which point the same SAE-bias diagnostic would apply to the expanded indication. Off-label drift between approvals is

addressed by Step 5 above, which uses postmarketing surveillance to compare the realized treated population to the disclosed target population and could be used to triggers penalties, label revisions, or investment in new clinical studies, if they diverge. Sponsors at the approval stage may have an incentive to specify the target population narrowly—narrower indications are easier to clear on safety and efficacy—and the postmarketing-surveillance would help close the residual gap from any tendency to understate the eventual treated population. The framework therefore does not require firms to forecast the long-run treated population perfectly; it requires them to disclose the labeled target at each approval and uses postmarketing data to discipline drift.

The regulatory structure outlined above echoes aspects of the FDA's 2024 draft guidance for ensuring race, ethnicity, sex, and age group diversity in trials.[19] The FDA guidance proposed that trials should pre-specify target levels of enrollment for each demographic group, and justify those goals: "enrollment goals should be informed by the estimated prevalence or incidence of the disease or condition in the U.S. intended use population" (U.S. Food & Drug Administration, 2024). Our proposed framework includes this structure of pre-specification and justification, while focusing attention on a risk index that is likely to predict the drug's safety risks. Further, our approach provides a quantifiable metric of predicted bias given the trial's enrollment patterns, for the safety risks commonly associated with cancer drugs. We depart from the FDA's proposed regulatory structure by suggesting a need for postmarket surveillance to ensure that trial sponsors have incentives to accurately specify the target population. An advantage of our approach is that it provides a single, clinically-relevant index for reporting trial enrollment, overcoming barriers associated with simultaneously monitoring enrollment across many dimensions.

There are alternative regulatory approaches that could also improve the external validity of trial SAE effects. Reweighting trial analyses so that participants match the target population on key characteristics could also help close the gap. Reweighting would still require a change to current practice, since trials rarely collect and report the relevant comorbidities that predict differences in SAE risk. Generally speaking, reweighting will also reduce the precision of the estimated effects (holding sample size fixed), and so would require more trial participants to achieve equivalent

[19]The draft guidance was removed from FDA.gov in January 2025 and later restored; FDA currently lists the document as draft guidance not for implementation.

power.

6.4 Magnitudes of Welfare Gains from SAE Regulation

A back-of-the-envelope calculation suggests that the welfare costs of current trial bias are meaningful relative to the minimal administrative burden of the framework proposed above. The assumptions required for this calculation are strong, so it should be taken as suggestive of order of magnitude benefits rather than a precise estimate. Details are presented in Appendix A5.

We quantify two channels through which correcting SAE bias generates welfare gains. First, we consider a physician decision-making channel: correcting average harm estimates would reduce prescribing at the margin, reclassifying patients whose baseline 1-year cancer mortality risk lies in a narrow band near the net-benefit threshold. We estimate the welfare gains from corrected SAE information through this channel at about $340 million per year. Second, we consider a marginal FDA approvals channel: corrected harm estimates would flip approval decisions for drugs whose population-average net benefit is barely positive under trial-based evidence. We estimate this channel at about $12 million per year. The combined estimate is about $350 million per year, mostly from better physician decision-making.

The information required to implement the framework—mean covariates in the trial and target populations—is modest, so the direct administrative cost is likely small relative to these welfare figures, although changing enrollment patterns to reduce SAE bias could impose additional recruitment, monitoring, or trial-design costs. Extending similar trial-representativeness regulation beyond oncology to FDA-reviewed prescription drugs and therapeutic biologics with comparable SAE intensity could yield benefits an order of magnitude larger, on the order of $9 billion per year, although this would require adapting our estimation approach to develop comparable models of SAE harm heterogeneity in those other settings (see Appendix A5.3 for details).

7 Conclusion

This paper finds that cancer patients who are at high risk of SAEs are substantially less likely to be enrolled in clinical trials, yet more likely to experience adverse events as a causal result of drug

treatment. There are several possible reasons for systematic underrepresentation of high SAE risk and high SAE treatment effect patients in trials. Pharmaceutical companies themselves may not want to enroll patients who are likely to develop complications. In addition, physicians enrolling patients in trials may be reluctant to enroll patients who would require additional monitoring or care. Patient preferences may also play a role; Alsan et al. (2024) finds that a history of underrepresentation may make patients reluctant to enroll, if they anticipate smaller benefits of participation.[20]

Assuming that improving the external validity of trials' estimated net benefits is a desirable goal, our results imply that current trials depart from this normative standard in systematic ways that regulators could monitor. Regulation would require new data collection on average rates of comorbidities in trials and target clinical populations. Our results do not speak to a broader question about the desirability of representativeness. If some types of patients are more costly to enroll than others, then there is a trade-off between representativeness and convenience sampling. Additionally, there are trade-offs between representativeness and statistical power: for example, it may be desirable to enroll patients at higher risk of the treated condition to maximize power to detect proportional treatment effects, at the expense of externally valid estimates of adverse events. These important issues are beyond the scope of our investigation here.

[20] Our results cannot separate these channels, although anecdotally, a pharmaceutical executive (who might be incentivized to blame other parties) privately emphasized the first channel as paramount.

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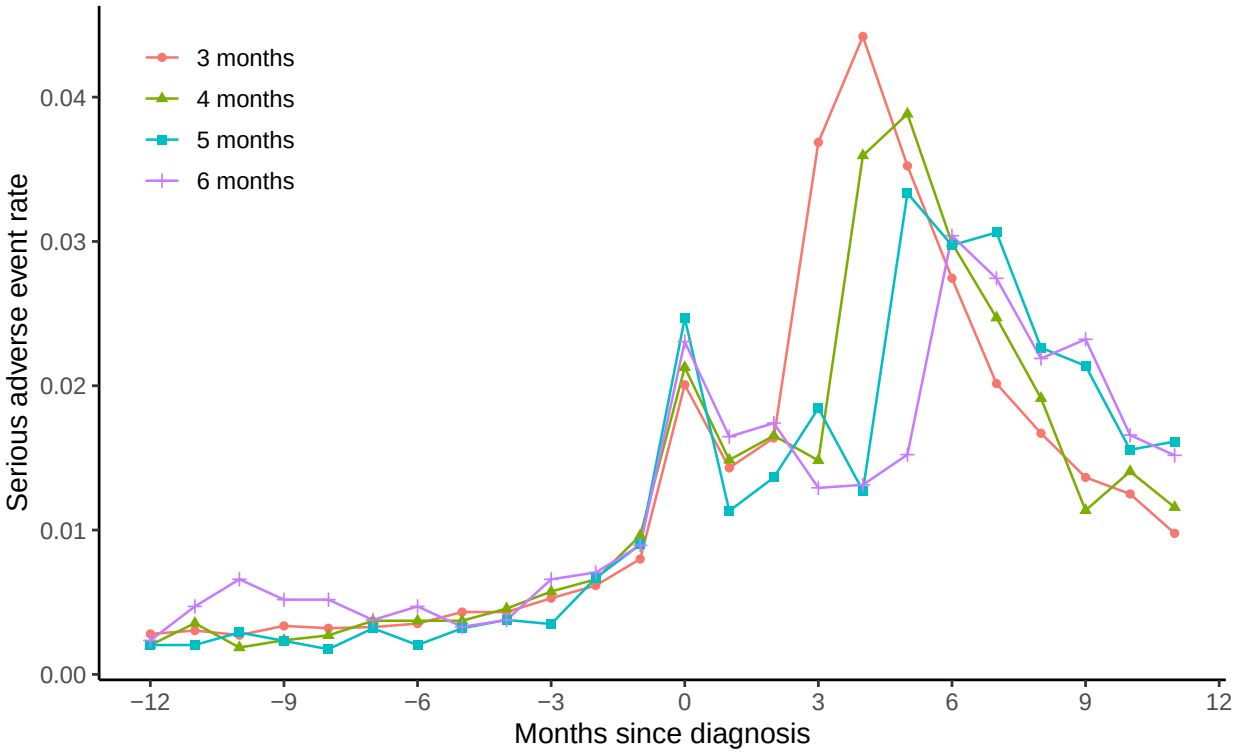
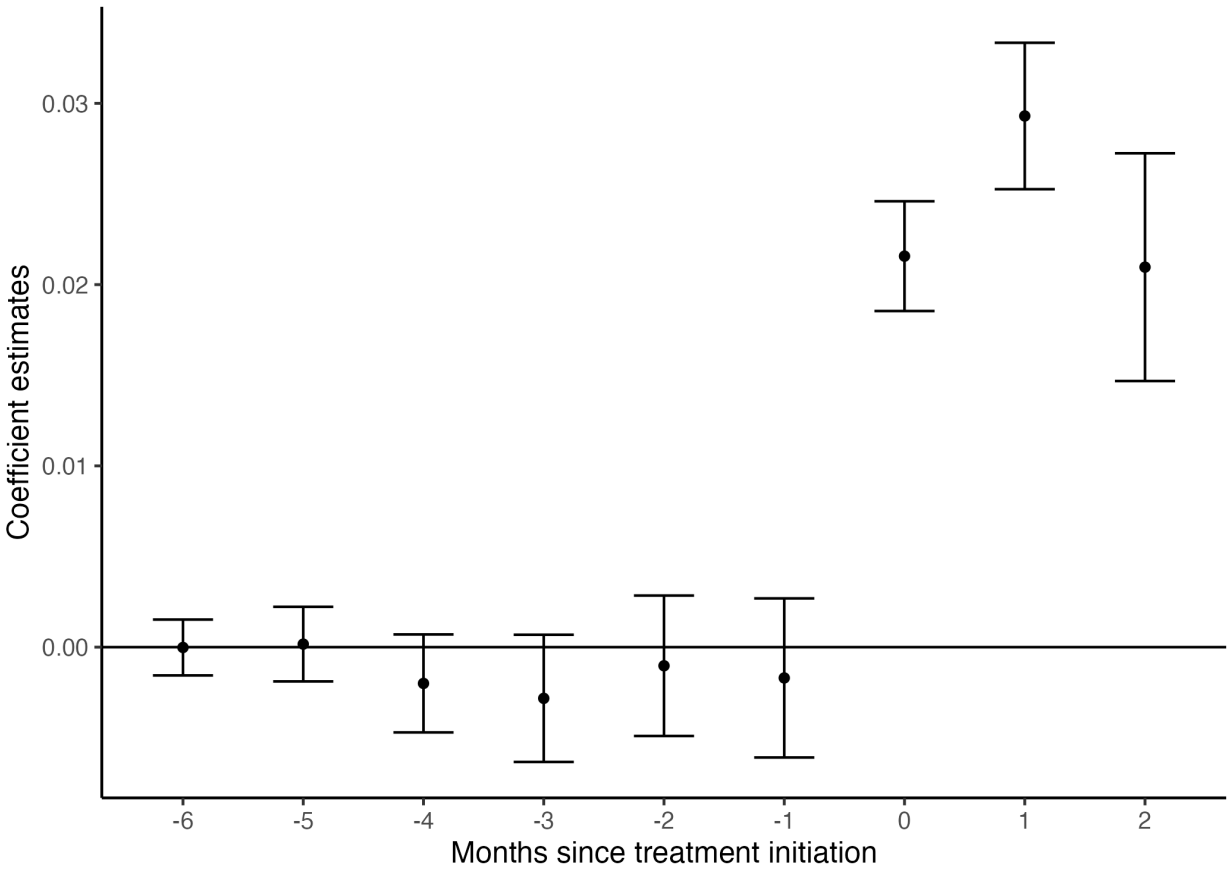
Figure 1: Trends in SAE Rates, Before & After Diagnosis



Notes: This figure shows the average SAE rate by month relative to diagnosis. The sample is split into 4 separate cohorts, corresponding to different timing of treatment initiation relative to diagnosis. The mean monthly SAE risk in the pre-diagnosis period is 0.0071. The SAE sample includes 24,002 patients.

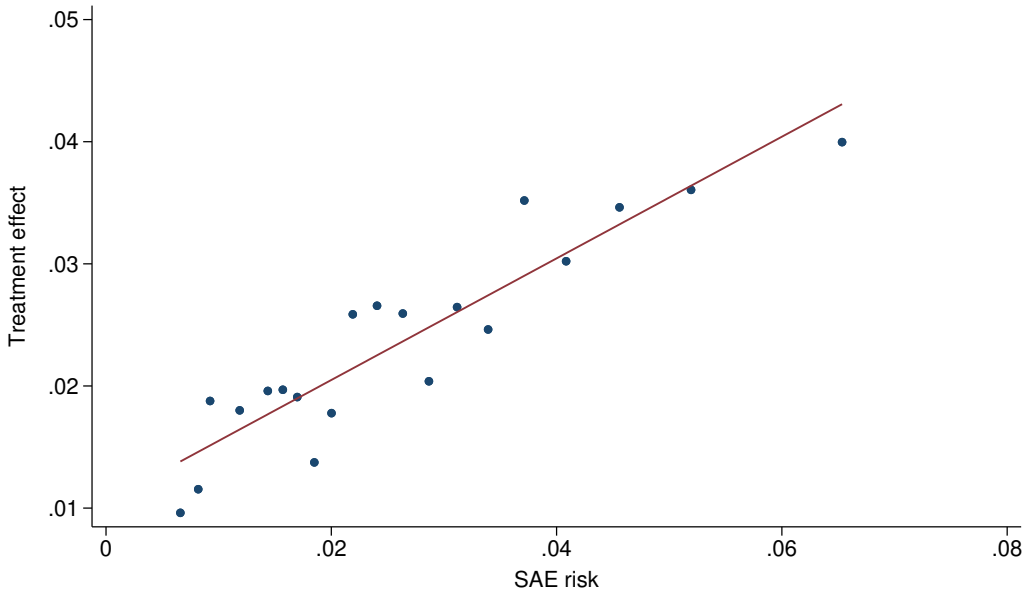
Figure 2: Event Study of SAE Rate, Before & After Treatment Initiation



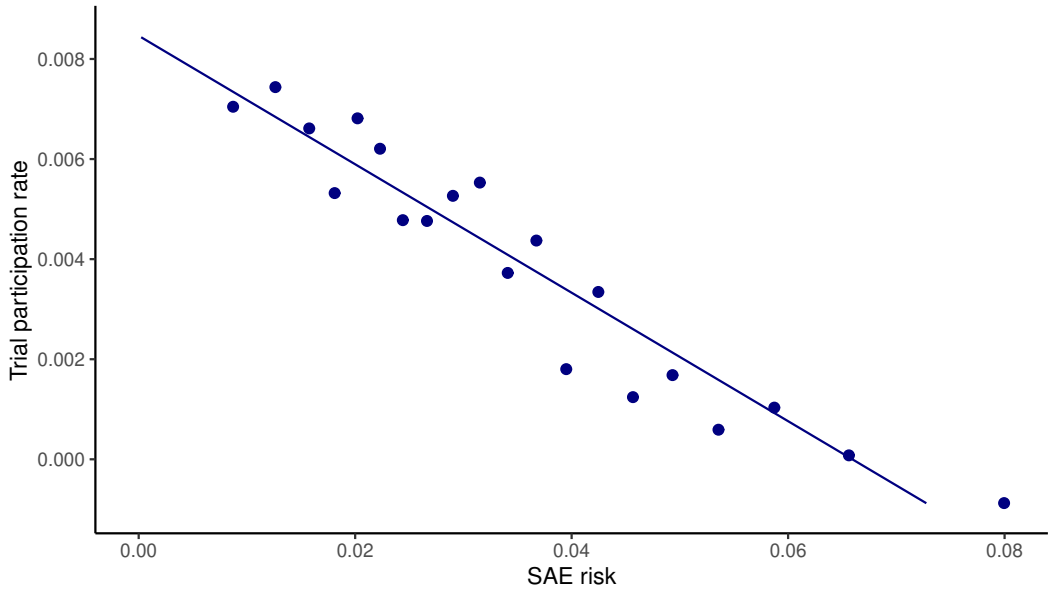
Notes: This figure displays coefficient estimates and 95% confidence intervals, for each month relative to treatment initiation. Pre-period coefficients come from estimating Equation 4; post-period values are averages of imputed treatment effects from the two-stage estimator. The outcome variable is a monthly indicator for any SAE. Control variables include fixed effects for: month since diagnosis, calendar time, treatment group (based on timing of treatment initiation 3, 4, 5, or 6 months after diagnosis), and cancer type by stage. We also control for patient age and predicted SAE risk. Confidence intervals are calculated using a GMM procedure following Gardner (2022), clustered at the patient level. The SAE sample includes 24,002 patients.

Figure 3: Predicted Risk of SAEs, Treatment Effects, and Trial Participation

(a) Relationship between Treatment Effect and Predicted Risk of SAEs



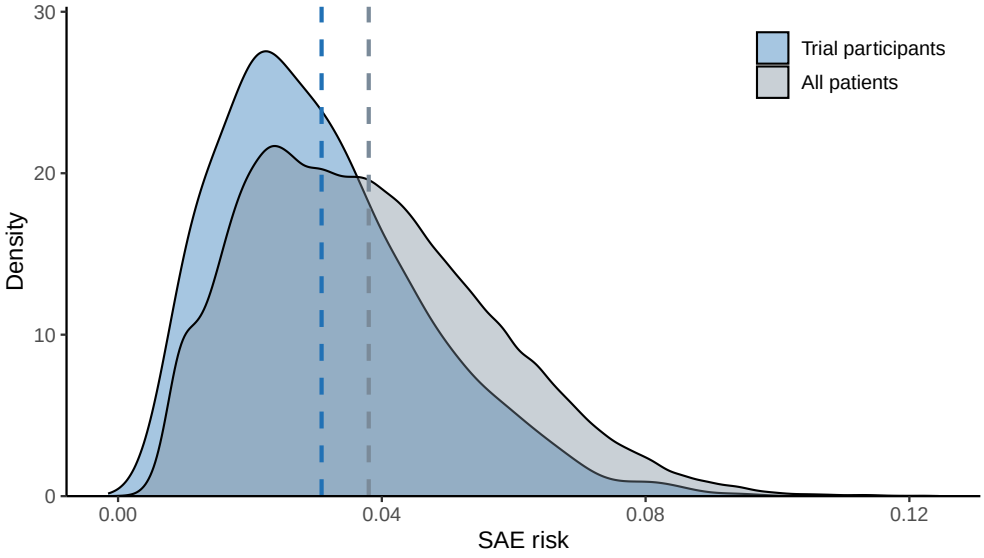
(b) Trial Participation and Predicted Risk of SAEs



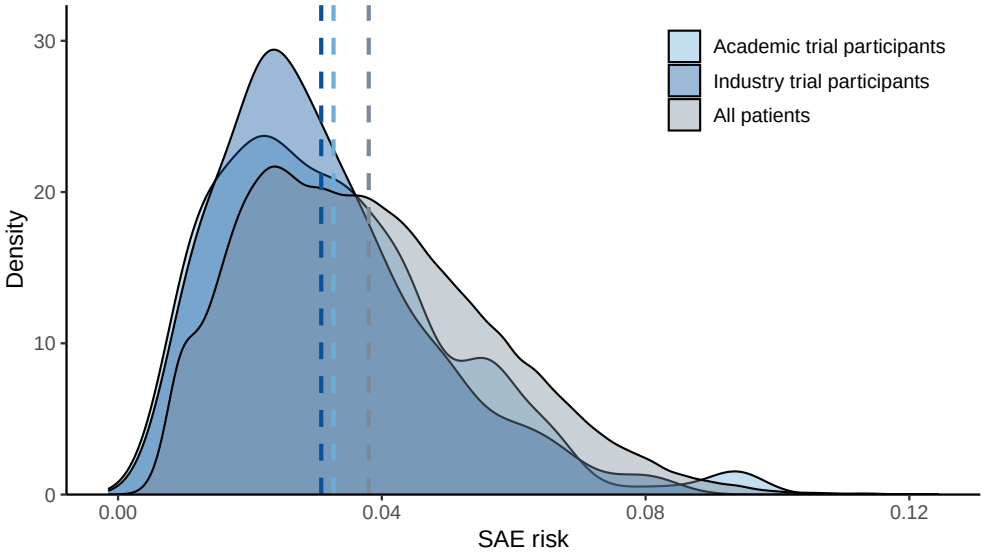
Notes: Both panels display binned scatterplots with 20 bins (with each bin representing 5% of the sample). Panel A displays the relationship between individual-specific treatment effect estimates $\hat{\theta}$ from Equation 4 (calculated for treated individuals) and predicted SAE risk. Predicted SAE risk is measured in a sample that holds out the index observation. The SAE sample includes 24,002 patients. Panel B displays the relationship between trial participation and SAE risk in the full trial-eligible cohort, where SAE risk has been centered at the mean risk among the adverse event cohort. The binned scatterplot controls for disease state, defined as the interaction of cancer type, stage at diagnosis, treatment line, and biomarkers. The Trial Participation sample includes 157,715 patients.

Figure 4: Distribution of Predicted SAE Risk Among Trial Participants vs. Full Cohort

(a) Trial Participants vs. Full Cohort



(b) By Trial Sponsor



Notes: Panel A displays kernel density plots of the SAE risk distribution among trial participants versus the full trial-participation sample. Panel B displays kernel density plots of the SAE risk distribution among industry- and academic-sponsored trial participants versus the full trial-eligible cohort. Trials are categorized according to the sponsor listed on ClinicalTrials.gov. In both panels, patients are re-weighted to match the distribution of specific disease cohorts for trial participants; disease cohorts are defined as the interaction of cancer type, stage at diagnosis, treatment line, and biomarkers. See Appendix Table A8. In Panel A, mean risk equals 0.0309 for trial participants and 0.0380 in the full cohort (p-value of difference $< .01$). In Panel B, mean risk equals 0.0308 for industry-sponsored trial participants, 0.0327 for academic-sponsored trial participants, and 0.0380 in the full cohort. (These differences are not statistically significant: p-value of difference in means between industry-sponsored vs. academic trial participants is $> .05$.) The Trial Participation sample includes 157,715 patients.

Table 1: Summary Statistics

	Adverse event cohort	Trial participation cohort	
	Treated in mo. 3-6	Non-participants	Trial participants
Age	74	75	72
Female	0.66	0.75	0.63
White	0.84	0.88	0.93
Black	0.09	0.07	0.04
Hypertension	0.74	0.81	0.73
Hyperlipidemia	0.74	0.81	0.74
Rheumatoid/osteoarthritis	0.50	0.58	0.51
Anemia	0.49	0.55	0.40
Ischemic heart disease	0.43	0.46	0.36
Cancer Types			
Bladder	X		
Breast	X	X	X
Colon	X		
Lung	X	X	X
Pancreas	X	X	X
Rectal	X		
Renal	X	X	X
Number of patients	24,002	156,863	852
Number of distinct trials			112

Notes: This table presents mean value of patient characteristics and summarizes the cancer types represented in the SAE and Trial Participation Samples.

Table 2: Differences between Trial Participants and Non-participants

	Non-participants	Trial participants	Absolute Difference	Adjusted Difference	
Female	0.75	0.63	-0.13	-0.01	
Kim frailty index	0.18	0.16	-0.02	-0.02	***
White	0.88	0.93	0.04	0.05	**
Black	0.07	0.04	-0.03	-0.03	**
Asian and Pacific Islander	0.04	0.03	-0.01	-0.01	
Age	74.7	71.7	-2.9	-2.7	***
Cataract	0.66	0.56	-0.11	-0.08	***
Diabetes	0.4	0.33	-0.07	-0.09	***
Ischemic heart disease	0.46	0.36	-0.09	-0.12	***
Depression	0.32	0.26	-0.05	-0.04	
Alzheimer's/dementia	0.1	0.04	-0.06	-0.05	***
Acute myocardial infarction	0.04	0.02	-0.01	-0.02	
Anemia	0.55	0.4	-0.15	-0.18	***
Asthma	0.16	0.12	-0.04	-0.04	*
Atrial fibrillation	0.14	0.09	-0.05	-0.06	***
Congestive heart failure	0.24	0.14	-0.1	-0.11	***
Chronic kidney disease	0.32	0.24	-0.08	-0.11	***
Chronic obstructive pulmonary disease	0.31	0.25	-0.07	-0.11	***
Glaucoma	0.25	0.21	-0.04	-0.03	
Hyperlipidemia	0.81	0.74	-0.07	-0.07	***
Hypertension	0.81	0.73	-0.08	-0.1	***
Benign prostatic hyperplasia	0.13	0.18	0.05	0	
Acquired hypothyroidism	0.31	0.21	-0.09	-0.07	***
Osteoporosis	0.24	0.14	-0.09	-0.06	***
Rheumatoid arthritis/osteoarthritis	0.58	0.51	-0.07	-0.05	*
Stroke/transient ischemia attack	0.13	0.06	-0.06	-0.07	***
Number of patients	156,863	852			

Notes: This table reports the differences in mean characteristics between trial participants and non-participants, in the Trial Participation Sample. The differences are adjusted for a patient's disease state (cancer type × stage at diagnosis × treatment line). Statistical significance of the adjusted difference is reported in the final column after Bonferroni correction. *** significant at the 1% level; ** significant at 5% level; * significant at the 10% level.

Table 3: LASSO Predictions of SAE Risk

A. LASSO Model Coefficients	
	Dependent variable:
Z-Standardized independent variables:	Average SAE Rate
Chronic kidney disease	0.0053
Kim frailty index	0.0050
Total chronic conditions	0.0035
Chronic obstructive pulmonary disease	0.0029
Hip fracture	0.0023
Hypertension	0.0018
Congestive heart failure	0.0018
Stroke/transient ischemia attack	0.0018
Anemia	0.0012
Acute myocardial infarction	0.0012
Benign prostatic hyperplasia	0.0006
Atrial fibrillation	0.0006
Rheumatoid arthritis/osteoarthritis	0.0004
Asthma	0.0004
Hyperlipidemia	0.0003
Ischemic heart disease	0.0000
Female	-0.0006
Osteoporosis	-0.0007
Glaucoma	-0.0008
Alzheimer's/dementia	-0.0009
Acquired hypothyroidism	-0.0009
Age^2	-0.0014
Sample size (n)	23,437
B. LASSO Predictions of SAE Risk	
Mean	0.036
Standard deviation	0.019
10th percentile	0.013
25th percentile	0.022
50th percentile	0.033
75th percentile	0.047
90th percentile	0.062

Notes: Dependent variable is a patient's monthly average occurrence of any severe adverse event during months 0, 1, and 2 following treatment initiation. Predictor variables were Z-standardized and reported in order of the coefficient. Fixed effects for 20 disease states (defined by cancer type and stage at diagnosis)were included in the regression and prevented from shrinkage by LASSO regularization. The following coefficients were dropped after regularization: age, cataracts, depression, and diabetes. Age was centered at 65 years. LASSO is estimated in the SAE Sample, excluding patients who initiated treatment after February 2020 because they lack complete three-month follow-up.

Table 4: Effect of Treatment Initiation on SAEs

	Dependent Variable: Serious Adverse Event			
	Model 1	Model 2	Model 3	Model 4
Post Treatment Initiation	0.024	0.024	0.024	0.024
	(0.0016)	(0.0016)	(0.0016)	(0.0016)
Post × (SAE Risk - $\overline{\text{SAE Risk}}$)		0.467		0.473
		(0.0652)		(0.0661)
ΔY for 1 SD higher SAE risk		0.008		0.008
		(0.001)		(0.001)
Calendar time	X	X	X	X
Time since diagnosis	X	X	X	X
Individual fixed effects			X	X
Number of patients	24,002	24,002	24,002	24,002
Number of observations	448,017	448,017	448,017	448,017

Notes: This table reports results from estimation of Eq. 2, estimating the effect of treatment initiation on the monthly SAE rate for 0–2 months after treatment initiation. We apply an imputation estimator that controls for fixed effects in: month since diagnosis, calendar time, treatment group (based on timing of treatment initiation 3, 4, 5, or 6 months after diagnosis), and cancer type by stage. In Models 1-2, we also control for patient age and predicted SAE risk. In Models 3-4, we include individual fixed effects. Models 1 and 3 average the individual treatment effect estimates from equation 4, and Models 2 and 4 regress the individual treatment effect estimates on patient-level demeaned risk of SAE (using the jackknifed risk model), as in equation 5. Confidence intervals are calculated via GMM following Gardner (2022), clustered at the patient level.

Table 5: Relationship between Trial Participation and SAE Risk: Logistic Regression

	Dependent Variable: Trial Participant		
	Full sample	Advanced stage cancers	Early stage cancers
Panel A. Controlling for Disease Cohorts Only			
SAE risk	-28.349	-26.875	-30.047
	(2.320)	(3.265)	(3.302)
% change in trial participation for 1 SD higher SAE risk	-40.7%	-38.2%	-41.5%
	(2.54)	(3.61)	(3.45)
Panel B. Controlling for Age, Sex, Race, and Disease cohorts			
SAE risk	-22.923	-25.111	-19.626
	(2.371)	(3.315)	(3.338)
% change in trial participation for 1 SD higher SAE risk	-34.5%	-36.2%	-29.5%
	(2.87)	(3.78)	(4.19)
Sample size	157,715	38,934	118,781

Notes: This table reports coefficients from logistic regressions where the outcome variable is Trial Participation and the key independent variable of interest is predicted SAE risk. Panel A reports the coefficient estimate and standard error of the SAE risk variable in a logistic regression controlling for 28 disease state fixed effects (cancer type × stage at diagnosis × treatment line Ã × biomarkers). Panel B reports the results from a logistic regression controlling also for age, age squared, sex, and race (White, Black, American Indian and Alaska Native, Asian and Pacific Islander, Other). Heteroskedastic robust standard errors are reported in parentheses.

ONLINE APPENDIX: Trials Avoid High Risk Patients and Underestimate Drug Harms

Jason Abaluck, Leila Agha, Sachin Shah

A1 Cohort construction & variable definitions

Adverse event cohort construction. The study cohort included bladder, breast, colon, lung, pancreas, rectal, and renal cancer patients in the SEER-Medicare database who met the following inclusion criteria: first diagnosed with local, regional, or distant cancer between January 2014 and December 2019, aged between 66 and 100 years old at diagnosis, continuously enrolled in Medicare Parts A/B/D from 1 year before to 1 year after diagnosis, and initiated treatment with any chemotherapy or immunotherapy 3 to 6 months after diagnosis in our baseline sample (we relax this window to 3 to 11 months in a robustness analysis). Linked Medicare claims extend back to January 2013, allowing us to record comorbidities and hospitalizations for 12 months prior to diagnosis. The sample is constructed to record monthly SAE hospitalizations for 12 months prior to diagnosis and 6 months afterwards. We end our sample period in February 2020 to exclude the Covid-19 pandemic.

Trial participation cohort construction. Following our previous study on trial participation (Shah et al., 2025b), a cohort of breast, lung, pancreatic, and renal cancer patients who met the following inclusion criteria was constructed from the SEER-Medicare database: first diagnosed with local, regional, or distant cancer between 2014 and 2019, aged 65 years or older at diagnosis, continuously enrolled in Medicare Parts A/B (and Part D if renal cancer patient) from 1 year before to 6 months after index date or until death. See Appendix Table A8 for details on included disease categories and inclusion criteria.

Cancer treatment. Carrier, Outpatient, and Part D event files were used to identify patients treated with a cancer drug. Cancer treatment was identified by HCPCS codes within the ranges J8501-J9999, C9000-9499, and Q0083-Q0085 and NDC codes for drugs categorized as a Chemotherapy or Immunotherapy in the SEER CanMED database.

Severe adverse events. We constructed a set of adverse events and ICD-9/10 codes that were used in previous studies of cancer treatment toxicity (Bishnoi et al., 2021; Bittoni et al., 2018; Du et al., 2005; Freedman et al., 2014; Gunturu et al., 2022; Hansen et al., 2014; Herbach et al., 2022; Hershman et al., 2013; Rashid et al., 2015; Reeder-Hayes et al., 2017; Sanoff et al., 2012; Wieder and Adam, 2023). A severe adverse event was defined as a hospitalization for which the primary

diagnosis was a potential adverse event. See Appendix Table A9 for a summary of SAE types.

A2 Model Derivation

This section provides a more detailed derivation of the model discussed in Sections 6.1 and 6. First, we describe our assumption for how trialists would change enrollment patterns to remove γ-bias (if required to do so). Consider a new trial with choice probabilities s_j and define $\Delta_j = s_j - p_j$, the difference between these probabilities and the population probabilities for each subgroup. In principle, any vector of perturbations Δ_j to the subgroup shares satisfying $\sum_j \Delta_j = 0$ and $\sum_j \Delta_j \gamma_j = 0$ will produce a new design which is γ-unbiased. We will specifically choose the perturbation Δ^* which is the weighted-L^2-minimal adjustment to the original (unconstrained) trial enrollment probabilities r_j. That is, we find Δ_j satisfying the two above constraints and minimizing the expression $\sum_j \frac{(\Delta_j - (r_j - p_j))^2}{p_j}$. This yields:

$$\Delta_j^* = (r_j - p_j) - \frac{B_\gamma p_j}{Var_p(\gamma)}(\gamma_j - E_p(\gamma)) \tag{A1}$$

where $E_p(\gamma) = \sum_j p_j \gamma_j$ and $Var_p(\gamma) = \sum_j p_j (\gamma_j - E_p(\gamma))^2$. Note that this minimization problem is identical if we write: $\tau_j = \beta_k(\alpha_j + \delta\gamma_j)$, adding a trial-specific scaling factor so that trialists who know α_j and γ_j still do not know net impacts. To ease notation, we assume $\beta_k = 1$ below.

Now we consider the implications of the new enrollment patterns for the external validity of the trial's estimated average net benefits. Let $h = \frac{Cov_p(\alpha,\gamma)}{Var_p(\gamma)}$, the population regression weighted coefficient of α on γ. Consider the case when $B_\alpha = \sum_j (r_j - p_j)\alpha_j$ (initial α-bias) and $B_\gamma = \sum_j (r_j - p_j)\gamma_j$ (initial γ-bias) have the same sign. The τ-bias of the original design is given by

$B_\alpha + \delta B_\gamma$. The bias of the new design is given by:

$$\begin{aligned} B_\tau(s) &= \sum_j (s_j - p_j)\alpha_j + \delta \cdot 0 \\ &= \sum_j [(r_j - p_j) + (s_j - r_j)]\alpha_j \\ &= B_\alpha - \frac{B_\gamma}{Var_p(\gamma)} \sum_j p_j(\gamma_j - E_p(\gamma))\alpha_j \\ &= B_\alpha - \frac{Cov_p(\alpha, \gamma)}{Var_p(\gamma)} B_\gamma \\ &= B_\alpha - hB_\gamma \end{aligned} \tag{A2}$$

where $Cov_p(\alpha, \gamma) = \sum_j p_j(\gamma_j - E_p(\gamma))\alpha_j$. We want to know if the old trial enrollment shares would generate more bias in average net benefits than the new enrollment shares, i.e.:

$$|B_\alpha + \delta B_\gamma| \geq |B_\alpha - hB_\gamma| \tag{A3}$$

Let $x = \frac{B_\alpha}{B_\gamma}$. We can rewrite A3 as $|x - h| \leq |x + \delta|$.

Since $x + \delta > 0$ when B_α and B_γ have the same sign, this is equivalent to satisfying both of the following two inequalities concurrently:

$$x - h \leq x + \delta \rightarrow -h \leq \delta \rightarrow \delta \geq -h \tag{A4}$$

$$-(x - h) \leq x + \delta \rightarrow h - x \leq x + \delta \rightarrow \delta \geq h - 2x \tag{A5}$$

Finally, that is equivalent to:

$$\max(-h, h - 2\frac{B_\alpha}{B_\gamma}) \leq \delta \tag{A6}$$

Note that if $h = 0$ (meaning that α_j and γ_j are uncorrelated), this always holds.

A3 Regulating SAE Risk and Net Impacts

We conduct a calibration exercise to assess whether eliminating the bias in SAE harms by adjusting enrollment as described in Appendix A2 above would result in trials with less bias in estimated net benefits, on average. More specifically, we are testing whether the condition in equation 9 is likely to hold in practice, in the context of cancer drug trials. This requires us to estimate h, the relationship between heterogeneous harms and benefits of treatment. Our empirical work in Section 4 estimated γ_p, the heterogeneous harms of cancer drugs. However, our quasi-experimental approach is not well-suited to estimating heterogeneous benefits of cancer drugs α_p, because survival benefits manifest over a longer time horizon and our approach leveraging variation in the timing of treatment initiation captures short-run differences in outcomes. Instead, we use our data to estimate cancer mortality risk, and assume that the drug's treatment benefits are proportional to this risk.

Calibration of heterogeneous treatment benefits proceeds in two steps. First, to estimate cancer mortality risk, we use the SEER data to predict mortality from cancer within 1 year of diagnosis. Variables used for prediction include tumor size, the number of positive regional lymph nodes, and treatment indicators for surgical or radiation treatment, and we control for primary tumor site and stage at diagnosis (local, regional, or distant). As expected, patients with larger tumors and those with more positive lymph nodes have higher cancer mortality risk, while patients receiving surgical treatment have lower mortality risk. Second, we estimate the proportional reduction in mortality from cancer drugs using clinical trial data. Specifically, we match the top 46 most commonly prescribed drugs in our sample to the clinical trials described on their FDA labels. We identify 66 randomized clinical trials reporting a survival endpoint (not all drugs report trials with mortality endpoints, but some drugs report more than one trial).[21] Across these 66 trials, we calculate an average 20.3% reduction in mortality in the treatment group relative to the control group. In our SAE sample, we estimate each patient's benefit of cancer drug treatment as a 20% reduction in their predicted 1-year cancer mortality risk.

[21] Some trials do not directly report 1-year outcomes but show Kaplan-Meier survival curves that include a 1-year horizon; we use pixel-counting to estimate mortality at the 1-year horizon.

To put our estimate of annual treatment benefits and monthly harms on a common cumulative scale, we scale up our monthly estimate of SAE treatment effects. Our baseline calibration multiplies the monthly SAE treatment effects by 3, to estimate the impact over the 3-month period following treatment initiation. This is conservative since many patients have longer durations of cancer drug treatment (beyond 3 months), and so continue to have elevated SAE hospitalization rates for more than 3 months; we compare this to alternative calibrations that multiply these SAE TEs by 6 or 12.

Next, using these measures of treatment benefits and harms, we estimate $Cov_p(\alpha, \gamma)$. We construct this measure using only variation in benefits and harms that arise conditional on the primary tumor site and cancer stage, since drug trials typically test for efficacy within a cancer site and stage. We find that $h = -0.0488$, suggesting only a weak relationship between SAE treatment effects and treatment benefits, whereby patients with a 10 percentage point (p.p.) greater probability of a drug-induced SAE event would experience a 0.5 p.p. greater decline in 1-year cancer mortality from treatment.

In our empirical work above, we presented evidence that B_γ is negative, i.e., trials understate the risk of drug-induced harms. We do not have direct evidence about the sign of B_α, but we suspect it is likely negative or zero if trials select patients who are likely to have greater benefits (consistent with trial sponsors' incentives to demonstrate that the drug is effective). Given that $h < 0$, if $B_\alpha \leq 0$, then comparing $-h = 0.049$ to δ is sufficient for checking the condition in equation 9. To calibrate δ, we turn to Shabaruddin et al. (2013), which summarizes evidence on the utility cost of drug-induced adverse events for cancer patients. The paper reports a mean utility with cancer of 0.88 (relative to 1 for healthy state and 0 if dead), and a utility decrement of -0.17 for the SAE hospitalization lasting 2–5 days, based on Beusterien et al. (2009). Thus, a SAE hospitalization corresponds to 0.193 times the utility cost of death ($0.193 = 0.17/0.88$). Since $-h = .049 < \delta = .193$, this implies that improving SAE representativeness would also improve representativeness in terms of net impacts. This remains true as long as SAE hospitalizations are at least 4.8% of the utility cost of death, but is no longer true below that threshold. If SAE hospitalizations are elevated for 6 rather than 3 months assumed at baseline, then $-h$ drops to $-h = .024$, thus suggesting improving

SAE representativeness would improve net benefit representativeness unless SAE hospitalizations were less than 2.5% of the utility cost of death.

If B_α and B_γ have opposite signs, so that current trial enrollment patterns *understate* drug benefits, then the condition is met as long as δ is sufficiently large and the total bias in benefits is substantially smaller than the total bias in harms. If $\delta = .19$, then magnitude of bias from understating benefits B_α under current enrollment patterns would have to be 12% or less of the bias from understating harms B_γ. This proportion decreases as δ shrinks, as reported in Table A18.

With sufficient data, the FDA could use analogous methods to the approach we develop here to try to regulate both α_j and γ_j representativeness concurrently. The analysis here suggests that, given reasonable assumptions about δ and B_α, regulating SAE representativeness alone is likely to improve net benefit representativeness in the setting of cancer drug trials.

A4 Alternative Regulatory Approaches: Simulation Design

We use simulations to compare two regulatory approaches to the status quo and to a representative-enrollment benchmark. The simulated estimand is the disease-state target-population average treatment effect of a new drug on SAE hospitalizations. The simulation focuses on the case in which SAE treatment-effect heterogeneity is correctly summarized by the predicted SAE risk index: individual treatment effects are linear in predicted baseline SAE risk, with the intercept and slope calibrated to match the empirical heterogeneous-effects model and the disease-state target-population average effect. Under this assumption, the simulation quantifies the bias reduction and precision cost of each approach, summarized by bias, power, coverage, and confidence-interval width.

For each eligible disease state with at least 30 observed trial participants, we construct the observed participant pool and target population from the trial-participation data. We further restricted to disease states with at least one observed trial participant in each of the 10 target-population SAE-risk deciles, to avoid failures of common support; these disease states are listed in the table note. We simulate randomized trials with 500 observations and 50% assigned to treatment arm.

We simulate four different trial enrollment and analysis approaches. Results are reported in

Table A1 below.

1. Status quo: samples from the observed participant pool and reports an unweighted difference in mean SAE rate.

2. Adjust enrollment shares: choose enrollment shares across 10 SAE-risk deciles to align the enrolled average SAE risk with the target-population average SAE risk. Enrollment shares are chosen to minimize distance from status quo enrollment shares subject to adding-up and nonnegativity constraints. Sample observed trial participants within each risk decile. Report the unweighted trial estimate. This corresponds to our main regulatory proposal described in Section 6.3.

3. Reweight trial results: keeps the original enrollment process but estimates treatment effects using risk-bin post-stratification weights over the same 10 SAE-risk deciles. This corresponds to the alternative regulation described in Section 6.3.

4. Representative oracle: draws directly from the target population and is included to contrast the precision cost of feasible policies.

Table A1: Policy simulation results among disease states with common support

Arm	Bias (p.p.)	Power (%)	Coverage (%)	Mean CI width (p.p.)
1. Status quo	-0.31	74.7	92.5	3.18
2. Adjust enrollment shares	-0.00	78.7	94.7	3.47
3. Reweight trial results	-0.02	59.5	94.6	4.42
4. Representative oracle	0.03	78.9	94.8	3.49

Notes: Bias is the average simulated trial estimate minus the disease-state target-population average treatment effect, reported in percentage points. Power is the share of simulated trials rejecting the null of no SAE effect at the 5 percent level. Coverage is the share of simulated 95 percent confidence intervals containing the true target-population effect. Mean CI width is the average width of the simulated 95 percent confidence interval, reported in percentage points. Results are equal-weighted across the 4 disease states with no structural or simulated support failure for any reported arm: regional, hormone receptor-positive breast cancer, first-line treatment for distant/metastatic non-small cell lung cancer, first-line treatment for distant/metastatic pancreatic cancer, and adjuvant treatment for regional-stage renal cancer. Simulations use trial size n = 500, and 1000 Monte Carlo replications per disease state.

A5 Welfare Magnitudes of SAE Regulation: Calculation Details

This appendix develops the two back-of-envelope calculations summarized in Section 6.4 to calculate the benefits of SAE regulation, and an order-of-magnitude extrapolation to non-oncology drugs.

A5.1 Physician decision-making channel

First, we estimate the welfare gain from physicians updating their treatment decisions after switching their SAE estimate from γ_{trial} to the target-population average γ_{target}. We conservatively assume homogeneity, ignoring the larger gains that could arise if physicians applied patient-specific SAE-risk predictions rather than only a corrected population average.

We assume physicians make treatment decisions by comparing medical benefits (proportional to mortality risk) with the SAE costs that we estimate. We further assume the treating physician has private information about each patient's mortality risk, and thus can assess patient-specific mortality more accurately than we can estimate from SEER-Medicare records. As a result, we do not expect treatment probabilities to switch from 0 to 1 at a strict threshold of modeled risk. Let q_i be patient i's baseline (untreated) 1-year cancer mortality risk and $y_i = \log q_i$. From observed covariates X_i, we estimate the conditional mean $\hat{y}_i = \mathbb{E}[y_i \mid X_i]$, so that true risk decomposes as:

$$y_i \;=\; \hat{y}_i + u_i, \qquad u_i \sim \mathcal{N}(0,\, \nu^2), \qquad u_i \perp \hat{y}_i, \tag{A7}$$

where $\hat{y}_i$ is our predicted log-risk and u_i is the physician's private information, with dispersion ν. We take the population of predictions to be log-normal, $\hat{y}_i \sim \mathcal{N}(\mu,\, \omega^2)$, so true risk is $y_i \sim \mathcal{N}(\mu,\, \omega^2 + \nu^2)$. Seeing y_i, the physician treats under regime r exactly when the true net benefit is positive, given the physician's information about average SAE treatment effects:

$$D_i^r \;=\; \mathbf{1}\{\, y_i > \log q_r \,\}. \tag{A8}$$

The baseline-mortality threshold q_r is the welfare cutpoint at which the true net benefit of treatment

changes sign under regime $r \in \{\text{trial, target}\}$:

$$q_r \;\equiv\; \frac{\delta\,\gamma_r\,T}{\rho}, \tag{A9}$$

where $\rho = 0.203$ is the average proportional mortality reduction from treatment, $\delta = 0.193$ is the death-equivalent utility cost of one SAE hospitalization, and $T = 3$ months is the baseline duration of acute SAE risk (see Appendix A3 for a discussion of how these parameter values are selected). With $\gamma_{\text{trial}} = 2.4$ and $\gamma_{\text{target}} = 2.8$ percentage points per month (Section 4.2), equation (A9) evaluates to baseline mortality cutoffs $q_{\text{trial}} \approx 6.85\%$ and $q_{\text{target}} \approx 7.99\%$.

Bounding the physician's private information. The physician may observe risk using information not available in our observed covariates ($\nu > 0$ in (A7)). We bound ν rather than estimate it, since our data includes mostly treated patients.[22] In prognostication studies, physicians rank mortality risk for a random patient who dies above mortality risk for a random patient who survives about 80% of the time (a "c-statistic" of 0.80) (Glare et al., 2003; Downar et al., 2017). These figures are specific to cancer and drawn largely from advanced-disease settings, where one-year mortality is high and predictable; in our broad treatment-initiation cohort the relevant physician accuracy is plausibly lower. A forecast this accurate has a log-risk dispersion of about 1.0 at our cohort's mortality rate, essentially equal to the dispersion of our own predicted risk, $\hat{\omega} = 1.01$. Physicians thus appear to have little prognostic information beyond our covariates, so our baseline takes the empirically central case $\nu \approx 0$ (with the exact value corresponding to a physician c-statistic = 0.80); for robustness, we also report welfare for values of ν between 0 and 1 (Table A3).

Welfare integral. The true per-patient net benefit of treatment at baseline log-risk y, valued under the bias-corrected harm γ_{target}, is

$$u(y) \;=\; \rho\left(e^{y} - q_{\text{target}}\right), \tag{A10}$$

[22] Lacking data on disease progression after diagnosis, we infer disease state from patients' treatment status. We do not directly observe the set of patients who have disease progression but choose not to receive systemic treatment.

which will be positive for $y > \log q_{\text{target}}$ and negative below this threshold. If eliminating bias in SAE treatment effect estimates moves the threshold from $\log q_{\text{trial}}$ to $\log q_{\text{target}}$, then physicians would switch the treatment status (from treated to untreated) for patients with true risk in the band $(\log q_{\text{trial}}, \log q_{\text{target}}]$. Every such patient has $y < \log q_{\text{target}}$ and hence $u(y) < 0$, so de-treating them is an unambiguous gain; averaging $-u(y)$ over the treated risk distribution gives the expected welfare gain per treated patient,

$$\Delta W \;=\; \int_{\log q_{\text{trial}}}^{\log q_{\text{target}}} \big(\delta\,\gamma_{\text{target}}\,T - \rho\,e^{y}\big)\, f\big(y;\,\mu,\sqrt{\omega^2+\nu^2}\,\big)\,dy \;>\; 0, \tag{A11}$$

where: $f(y;\,\mu,\sqrt{\omega^2+\nu^2})$ is the density of *true* risk among treated patients; (μ,ω) are the mean and standard deviation of our predicted log-risk in the treated cohort (estimated as $\hat{\mu} = -2.24$ and $\hat{\omega} = 1.01$); and ν is the physician's private-information dispersion.

Estimation from SEER–Medicare. We obtain $\hat{y}_i$ by predicting 1-year mortality from claims covariates on the SEER–Medicare SAE cohort among treated individuals. Assuming treatment effects are proportional to mortality risk (as in Appendix A3), $\tilde{q}_i = (1-\rho)\,q_i$ rescales a predicted treated risk $\hat{\tilde{q}}_i$ to the corresponding untreated risk, and

$$\hat{y}_i \;=\; \log\!\Big(\frac{\hat{\tilde{q}}_i}{1-\rho}\Big). \tag{A12}$$

We observe $\hat{y}_i$ for the treated cohort.

Aggregation to dollars. The de-treated patients are the treated patients whose risk falls in the band with marginal net benefits of treatment. The gain aggregates over the Medicare-age treated count $N_t = 383{,}500$ per year (National Institutes of Health, 2024; American Cancer Society, 2026) directly:

$$\$_{\text{ann}} \;=\; N_t \cdot \Delta W \cdot \text{VSL}, \tag{A13}$$

where ΔW is the per-treated-patient gain from equation (A11) and the value of a statistical life is \$13.2 million (U.S. Department of Transportation, 2023); all welfare figures in this appendix are

reported in 2023 dollars. Evaluating ΔW on the treated predicted-risk distribution, about 5.7% of treated patients fall in the band. Substituting into equation (A13) gives an annual gain of $340 million (Table A2); the estimate depends modestly on the assumption about physicians' forecast accuracy ν (see Table A3) and scales linearly in N_t and the VSL (see Table A4).

Table A2: Physician decision-making channel: data-driven band mass

Quantity	Value
$\hat{\omega}$ (sd of predicted log-risk, treated)	1.01
Band share $\Pr(\log q_{\text{trial}} < y \leq \log q_{\text{target}})$	5.7%
Treated count N_t (per year)	383,500
VSL	$13.2M
Annual welfare gain	$340M

Notes: Predicted 1-year baseline mortality risks $\hat{q}_i = \hat{p}_i/(1-\rho)$ come from a ridge-penalized logistic of observed 1-year mortality on disease state, tumor size, nodal status, age, sex, and year of diagnosis (SAE sample, $N = 24{,}002$). $\hat{\omega} = \text{sd}(\log \hat{q}_i)$. Band share is the fraction of treated patients with $\hat{q}_i \in (q_{\text{trial}}, q_{\text{target}}] = (6.85\%, 7.99\%]$ under a $N(\hat{\mu}, \hat{\omega}^2)$ fit to the predicted-risk distribution. Annual gain $= N_t \cdot \Delta W \cdot \text{VSL}$ from equation (A13).

Table A3: Sensitivity of the physician-channel welfare gain to private information ν

Physician private information ν (log-risk sd)	0	0.25	0.50	0.75	1.00
Implied physician c-statistic	0.81	0.81	0.83	0.86	0.88
De-treatment band share	5.7%	5.6%	5.2%	4.7%	4.2%
Welfare gain, $M/yr	340	331	309	280	250

Notes: Columns vary the dispersion of the physician's private information ν over $[0, 1]$. Because ν is not identified from the treated-only sample, we bound it using external physician forecast-skill evidence. True log baseline risk is $y \sim N(\hat{\mu},\, \hat{\omega}^2 + \nu^2)$ with $\hat{\mu} = -2.24$ and $\hat{\omega} = 1.01$ (Table A2), so larger ν widens the true-risk distribution. The implied physician c-statistic is the discrimination of a calibrated log-normal forecast whose log-risk dispersion is $\sqrt{\hat{\omega}^2 + \nu^2}$, computed by simulation; the prognostication literature centers on $c \approx 0.80$ (Glare et al., 2003; Downar et al., 2017), so $\nu \approx 0$ is the empirically central case and $\nu = 1$ ($c \approx 0.88$) a deliberately generous upper bound. The de-treatment band share is the mass of $N(\hat{\mu}, \hat{\omega}^2 + \nu^2)$ in $(\log q_{\text{trial}}, \log q_{\text{target}}] = (6.85\%, 7.99\%]$. The annual welfare gain equals $N_t \cdot \Delta W \cdot \text{VSL}$ (A13).

Table A4: Physician decision-making channel: sensitivity analysis

Scenario	Older treated patients/year	VSL ($M)	Annual value ($M)
Central	383,500	13.2	202
Lower VSL	383,500	7.9	121
Higher VSL	383,500	18.5	283
Fewer treated patients	300,000	13.2	158
More treated patients	500,000	13.2	263

Notes: Each row varies one input – annual older treated patients N_t or the value of a statistical life (VSL) – holding the other at the Central value. Annual value $= N_t \cdot \Delta W \cdot \text{VSL}$ (A13), with ΔW evaluated at the baseline $\nu = 0$ (log-risk dispersion $\hat{\omega} = 1.01$). Central N_t from National Institutes of Health (2024) (650,000 chemotherapy patients/year) and American Cancer Society (2026) (59% age 65+); VSL central and range from U.S. Department of Transportation (2023).

A5.2 Marginal drug approvals channel

Next, we quantify how often correct estimation of SAE risk would move a drug from barely positive to barely negative net benefit for the target population, and thus potentially change approval decisions. The correction shifts net benefit downward by the same death-equivalent amount per treated patient.

For a drug with population-average benefit Δm and population-average SAE treatment effect γ per month, the model's approval condition is $\Delta m > \delta \cdot \gamma \cdot T$. The trial-based and bias-corrected approval thresholds, expressed as absolute 1-year mortality reductions, are

$$\Delta m_{\text{trial}} \;=\; \delta \cdot T \cdot \gamma_{\text{trial}} \;=\; 0.193 \times 3 \times 0.024 \;\approx\; 1.39 \text{ pp},$$

$$\Delta m_{\text{target}} \;=\; \delta \cdot T \cdot \gamma_{\text{target}} \;=\; 0.193 \times 3 \times 0.028 \;\approx\; 1.62 \text{ pp}.$$

FDA approval decisions often consider hazard ratios (HR), so we translate Δm into an overall-survival hazard ratio under a proportional-hazards model: $\text{HR} = \ln(1 - m_0 + \Delta m)/\ln(1 - m_0)$, where m_0 is the 1-year baseline cancer mortality in the target population. At a central calibration of $m_0 = 25\%$, the marginal-approval band corresponds to HRs in $[0.926, 0.936]$.

Elbaz et al. (2024) report the empirical HR distribution. Of 392 FDA oncology approvals between 2006 and 2023, 78% rest on surrogate rather than overall-survival endpoints; the median HR among the 88 OS-based approvals is 0.71 (IQR 0.66–0.78), while the median HR among the 153 approvals with post-approval OS data is 0.78 (IQR 0.67–0.89). Because truly marginal approvals are more likely to be surrogate-based than OS-proven, our central calculation uses the wider post-approval HR distribution, approximated as Normal$(0.78, 0.163)$ with standard deviation derived from the IQR. Integrating this distribution over the marginal HR band $[0.926, 0.936]$ yields an implied marginal share of 1.68% of approvals (Del Paggio et al., 2021; Olivier et al., 2021; Elbaz et al., 2024).

The Elbaz sample implies 24 oncology indication approvals per year over 2006–2023. The marginal share of 1.68% means 0.40 marginal approvals per year, with a steady-state stock of $0.40 \times 4 \approx 1.6$ marginal approvals on the market at any time (assuming a 4-year correction lag

before post-market evidence brings harm estimates into alignment with their true magnitude). Naci et al. (2025) find that an FDA accelerated approval in oncology reaches roughly 2,000 Medicare beneficiaries over its period of uncertain benefit, or about 500 per year over a 4-year window. An independent SEER–Medicare analysis of newly approved oncology drugs implies a similar order of magnitude (Green et al., 2021). With approximately 500 Medicare-age patients treated per marginal approval per year and an average welfare loss of $\frac{1}{2}\delta T(\gamma_{\text{target}} - \gamma_{\text{trial}}) \approx 0.00116$ death-equivalents per treated patient, valued at \$13.2 million per statistical life (U.S. Department of Transportation, 2023), the marginal-approvals welfare cost is

$$1.6 \times 500 \times 0.00116 \times \$13.2\text{M} \;\approx\; \$12 \text{ million per year},$$

or about 0.9 statistical death-equivalents per year. Table A5 reports the implied annual welfare cost across alternative assumptions for the HR distribution, approval rate, treated-patient count per approval, correction lag, and VSL.

The 3-month duration of acute SAE risk used throughout matches the paper's main quasi-experimental post-period and is conservative. If the trial–target SAE gap persists for 6 or 12 months instead, both channels grow, but at different rates (Table A6). In the physician channel, the reclassification band shifts upward into the upper tail of the predicted-risk distribution, so the share of treated patients reclassified is roughly flat and then falls. This channel scales close to linearly (about 2× at 6 months and 2.6× at 12 months). In the approvals channel, the marginal hazard-ratio band instead widens and shifts toward the dense median of the empirical HR distribution, so the share of marginal approvals rises steeply; combined with the larger per-case loss, that channel scales much faster than linearly (about 5× and 20×). Table A6 reports this duration sensitivity. We treat the 3-month value as the preferred estimate, since the paper's quasi-experimental evidence is strongest over that horizon, and report longer durations as upper bounds.

The combined estimate across the two channels is about \$350 million per year (\$340M physician channel from Table A2 plus \$12M marginal-approvals channel from Table A5). The most robust qualitative conclusions are (i) the physician decision-making channel dominates under the paper's 3-month SAE-bias horizon, with the marginal-approvals channel roughly an order of mag-

nitude smaller; and (ii) the marginal-approvals channel becomes substantially larger if the SAE bias persists beyond 3 months or if marginal approvals reach much larger treated patient volumes.

Table A5: Marginal drug approvals channel: sensitivity analysis

Scenario	Approvals /year	Marginal share	Patients /yr/approval	Lag (yrs)	VSL ($M)	Annual value
Central	24	1.68%	500	4	13.2	$12M
OS-approval HR distribution	24	0.22%	500	4	13.2	$1.6M
Higher 2024 approval count	53	1.68%	500	4	13.2	$27M
Fewer patients per approval	24	1.68%	250	4	13.2	$6M
More patients per approval	24	1.68%	1,000	4	13.2	$25M
3-year correction lag	24	1.68%	500	3	13.2	$9M
5-year correction lag	24	1.68%	500	5	13.2	$15M
Lower VSL ($7.9M)	24	1.68%	500	4	7.9	$7M
Higher VSL ($18.5M)	24	1.68%	500	4	18.5	$17M

Notes: Annual value equals (approvals/year) × (marginal share) × (correction lag) × (patients/year per approval) × $\frac{1}{2}\delta T(\gamma_{\text{target}} - \gamma_{\text{trial}}) = 0.00116$ death-equivalents per patient × VSL. Central marginal share computed by integrating Normal$(0.78, 0.163)$ over the HR band $[0.926, 0.936]$ using the post-approval HR distribution from Elbaz et al. (2024). Central approval count from Elbaz et al. (2024) (392 approvals over 2006–2023); 53/year alternative from U.S. Food and Drug Administration, Oncology Center of Excellence (2024). VSL central and range from U.S. Department of Transportation (2023). Central patients per marginal approval (≈500 per year, ≈2,000 over the 4-year window) from Naci et al. (2025), corroborated by Green et al. (2021).

Table A6: Sensitivity to the assumed duration of the trial–target SAE bias, by channel

Assumed duration (months)	Physician welfare ($M)	Physician band share	Approvals welfare ($M)	Approvals marginal share	Combined ($M)
3 (baseline)	340	5.7%	12	1.68%	352
6	700	5.8%	65	4.43%	765
12	900	3.7%	273	9.29%	1,173

Notes: Each row assumes the trial–target SAE gap persists for the stated number of months, so the per-patient death-equivalent bias is proportional to duration; other inputs follow the central scenarios in Tables A2 and A5. "Physician band share" is the mass of the predicted-risk distribution in the reclassification band $(q_{\text{trial}}, q_{\text{target}}]$; "approvals marginal share" is the share of approvals in the marginal HR band.

A5.3 Order-of-magnitude extrapolation to all prescription drugs

The estimates above apply specifically to cancer drugs, as prescribed to older adults (age 65+). As an order-of-magnitude extrapolation, we ask what the welfare benefits of analogous trial-representativeness regulation might be if extended to all FDA-reviewed prescription drugs and therapeutic biologics.

Approval channel scaling. The FDA's Center for Drug Evaluation and Research approved 50 novel drugs in 2024 (U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 2024), against 19 novel oncology approvals reported by the Oncology Center of Excellence (U.S. Food and Drug Administration, Oncology Center of Excellence, 2024). All-drug novel-approval flow is therefore roughly 2.6 times the oncology novel-approval flow, before counting biologics (separately regulated by the FDA Center for Biologics Evaluation and Research) or major label expansions. Scaling our oncology approval-channel estimate of $12 million per year by this approval flow yields a baseline all-drug approval-channel estimate of $31 million per year.

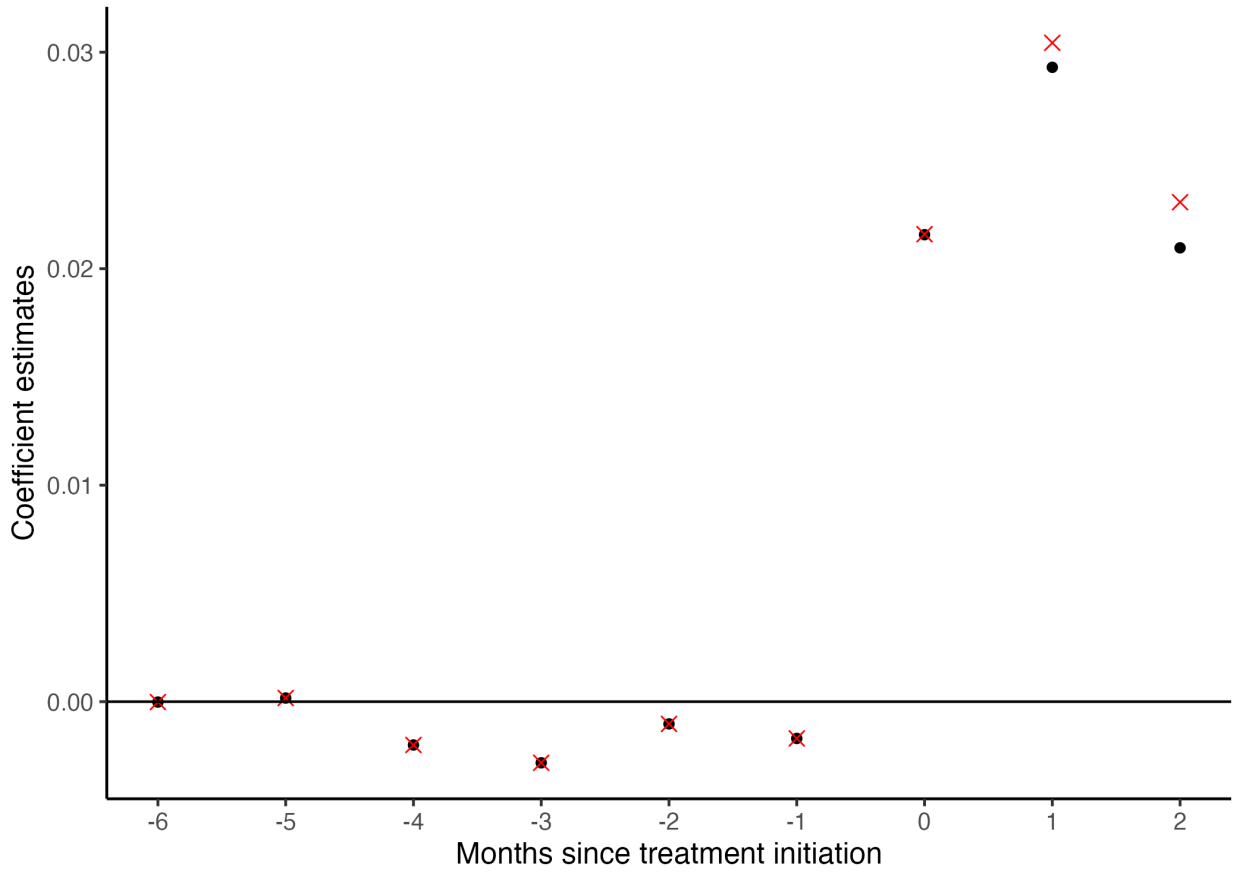
Physician channel scaling. The oncology treatment decision channel calculation yields $340 million per year of welfare loss from incorrect SAE estimates, with approximately 383,500 Medicare-age systemically treated cancer patients, or $886 per treated patient per year. Most prescription-drug therapy bears substantially lower acute-SAE risk than systemic cancer therapy, so we restrict the extrapolation to drug categories with plausibly comparable SAE intensity: chronic anticoagulants, biologics and disease-modifying antirheumatic drugs for autoimmune disease, and chronic immunosuppression following organ transplant. These categories together cover on the order of 10 million U.S. adult patients per year. Applying the oncology per-treated-patient welfare gain uniformly within these classes gives

$$10\text{M patients} \times \$886 \approx \$8.9 \text{ billion per year.}$$

Combined estimate and caveats. Combining the two channels, the baseline all-drug extrapolation is approximately $8.9 billion per year, principally from the physician decision-making channel restricted to comparable SAE drug classes. These estimates are necessarily rough: we do not estimate the magnitude of selection on SAE risk outside oncology; the density of approval and treatment decisions near the net-benefit threshold is poorly characterized in non-oncology settings; the 3-month treatment duration when SAEs may occur could be too narrow for chronic-drug settings; and any prospective regime would diffuse only gradually through trial designs, labels, guidelines, payer rules, and prescribing norms.

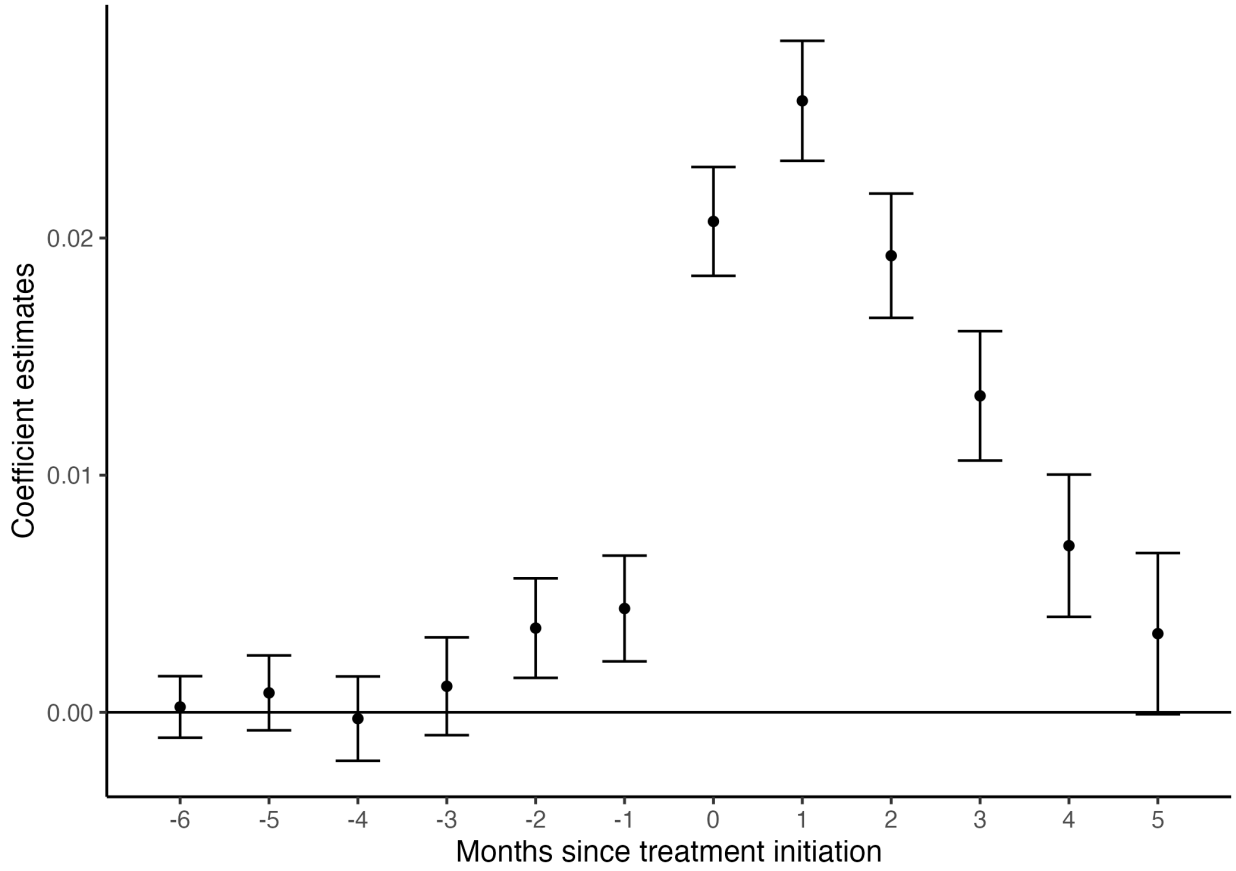
A6 Additional Figures & Tables

Figure A1: SAE Rate, Before & After Treatment Initiation:
Censoring Patients after Death



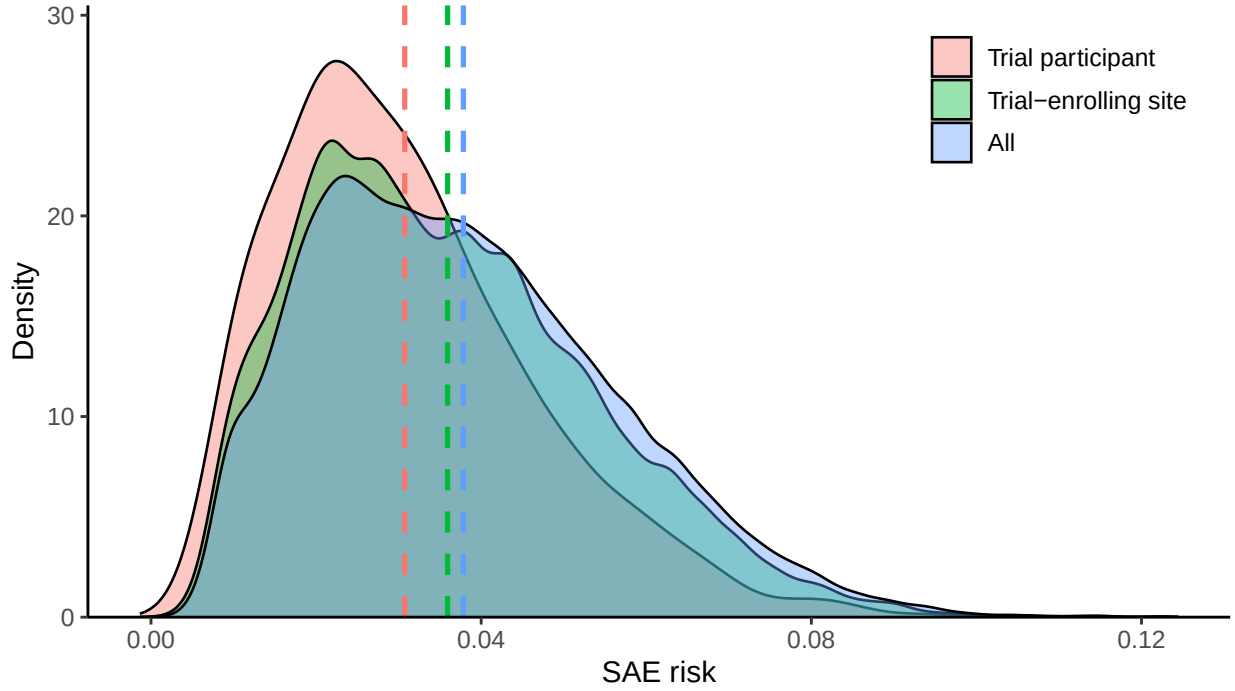
Notes: This figure reports the coefficients $\hat{\theta}^R$ from Equation 6 in the main SAE sample described in the text, initiating treatment 3-6 months after diagnosis. The black dots reflect our baseline estimates, while the red X's display results from an alternative sample that drops patients from the sample in months after their death. 3.47% of patients who initiated treatment in months 3-6 died within 5 months since diagnosis.

Figure A2: SAE Rate, Before & After Treatment Initiation:
Broad Cohort with Treatment Initiation in Months 3-11



Notes: This figure reports the coefficients $\hat{\theta}^R$ from Equation 6 using a broader cohort of patients than the baseline analysis. Specifically, this analysis expands to include all patients who initiate treatment within 3-11 months following diagnosis (instead of restricting to cohorts initiating treatment 3-6 months following diagnosis, as in the main analysis).

Figure A3: Distribution of SAE Risk Among Trial Participants vs. Full Cohort by Practice Enrollment Status



Notes: This figure displays kernel density plots of the SAE risk distribution for three groups: trial participants; patients receiving care at trial-enrolling sites; and all patients. The kernel density for patients receiving care at trial-enrolling sites is reweighted to match the joint distribution of disease cohorts and trial sites among trial enrollees; thus trial sites contributing a greater share of trial enrollees are weighted more heavily. The kernel density for the full patient cohort ("all") is reweighted to match the distribution of disease cohorts among trial enrollees. Disease cohorts are defined as the interaction of cancer type, stage at diagnosis, treatment line, and biomarkers (see Appendix Table A8). Mean risk equals 0.0307 for trial participants, 0.0342 for patients in trial-enrolling sites, and 0.0353 among all patients attributed to a practice. To ensure comparability of the three samples, we restrict this analysis to the 88% of patients in the Trial Participation Cohort who could be matched to their plurality oncology practice (to define their site of care); accordingly, we have 833 trial participants, 64,491 patients at trial-enrolling sites, and 138,403 total patients.

Table A7: SEER Registries

California
Connecticut
Georgia
Hawaii
Idaho
Iowa
Kentucky
Louisiana
Massachusetts
Detroit (Metropolitan)
New Jersey
New Mexico
New York
Texas
Utah
Seattle (Puget Sound)

Notes: This table lists the geographic sites of all the SEER Registries included in our analysis.

Table A8: Trial-eligible cohort disease state definitions (Part 1)

Cancer Type	Neoadjuvant/Adjuvant	Advanced
Breast	**Trials for neoadjuvant/adjuvant breast cancer were included.** **Patients**: We included all patients with local or regional disease at diagnosis. We constructed 8 cohorts based on 4 biomarker possibilities (HER2+/HR−, HER2−/HR+, HER2+/HR+, triple negative) and 2 stage possibilities (local, regional). Index date is diagnosis date.	**Trials for advanced-stage breast cancer were not included** because significant heterogeneity in therapeutic options and criteria for clinical trial eligibility for patients with advanced-stage disease increases the risk that we misattribute patients as potential trial participants who do not have the disease state studied in the trial. **Patients**: Excluded patients with distant disease at diagnosis.
Lung	**Trials for neoadjuvant/adjuvant lung cancer were not included** because many trials were specifically for patients who did or might get surgical resection, while others were for patients getting chemoradiation, and registry data do not provide imaging data necessary to identify patients appropriate for surgery vs radiation. Thus, there would be higher misattribution than in other neoadjuvant/adjuvant categories. **Patients**: Excluded patients with local or regional disease at diagnosis and no drug claims qualifying them for the advanced-stage cohort (as defined in the "Advanced" column).	**Trials for advanced-stage lung cancer were included.** **Patients**: We constructed 4 separate cohorts for Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC), differentiating first vs. second line treatment cohorts. Patients must have received a drug from the relevant drug list. Drug list for NSCLC*: pemetrexed, paclitaxel, paclitaxel protein-bound, etoposide, docetaxel, gemcitabine, pembrolizumab, nivolumab, vinorelbine, atezolizumab Drug list for SCLC*: etoposide, irinotecan, atezolizumab, lurbinectedin, topotecan First line: If diagnosed with distant disease, start any listed drug on or after diagnosis date. If diagnosed with local or regional disease, then first-line treatment requires drug claim to begin $\geq$180 days after diagnosis. Second line: Start a new drug after the final claim of first-line drug(s). Index date is the earlier of the date of treatment initiation (for relevant treatment line) or first report of relevant RCT participation. * Note: platinum chemotherapies are excluded from these drug lists as they are generally used in conjunction with other drugs and are sometimes re-used in subsequent lines of therapy, increasing the risk of misattribution of line of therapy.

Table A8: Trial-eligible cohort disease state definitions (Part 2)

Cancer Type	Neoadjuvant/Adjuvant	Advanced
Pancreatic	**Trials for neoadjuvant/adjuvant pancreatic cancer were included.** **Patients**: Any patients with local or regional disease at diagnosis. Index date is diagnosis date.	**Trials for advanced-stage pancreatic cancer were included.** **Patients**: We differentiated first vs. second line treatments using claims data as described below. Patient must be receiving a drug from the relevant drug list (see below). Patients must have distant disease at diagnosis. Drug list: paclitaxel, paclitaxel protein-bound, gemcitabine, irinotecan, oxaliplatin, capecitabine, fluorouracil. First line: Start any listed drug on or after diagnosis date. Second line: Start a new drug after the final claim of first-line drug(s). Index date is the earlier of the date of treatment initiation (for relevant treatment line) or first report of relevant RCT participation.
Renal	**Trials for neoadjuvant/adjuvant renal cancer were included.** **Patients**: Any patients with local or regional disease at diagnosis. Index date is diagnosis date.	**Trials for advanced-stage renal cancer were included.** **Patients**: We studied only first-line treatments. Patients must be receiving a drug from the drug list (see below). Patients must have regional or distant disease at diagnosis. Drug list: sunitinib, cabozantinib, nivolumab, ipilimumab, pazopanib, axitinib, everolimus, lenvatinib, sorafenib, temsirolimus. First line: Start any listed drug on or after diagnosis date. Index date is the earlier of the date of treatment initiation or first report of relevant RCT participation.

Table A9: Proportion of patients with a SAE within 3 months of treatment initiation, by SAE type

Any	0.1035
Infection	0.0528
Hematologic	0.0219
Kidney	0.0169
Gastrointestinal	0.0115
Cardiac	0.0075
Lung	$\leq$ 0.0005
Liver	$\leq$ 0.0005
Number of patients	24,002
Number of observations	69,140

Notes: This table lists the rate of having at least one hospitalization for a potential SAE of each listed subtype. The sample includes 24,002 unique patients and 69,140 patient-month observations from 0–2 months from treatment initiation.

Table A10: Trials by Tumor Site and Trial Phase

Tumor site	Phase 1	Phase 2	Phase 3	Phase 4	Total
Breast	0	12	13	0	25
Lung	1	13	24	1	39
Pancreatic	0	21	9	0	30
Renal	2	2	14	0	18
Total	3	48	60	1	112

Notes: This table lists the number of included trials by site and trial phase.

Table A11: Trial Characteristics

Tumor site	N	Industry sponsored	Cited in FDA approval
Breast	25	0.32	0.12
Lung	39	0.82	0.23
Pancreatic	30	0.60	0.00
Renal	18	0.61	0.28
Overall	112	0.62	0.15

Notes: This describes characteristics of trials included in our analysis. Industry sponsorship is ascertained from the ClinicalTrials.gov record for each trial. Citations of the trial in FDA approval documentations were found by searching records for each NCT number, with assistance from Codex.

Table A12: Effect of Treatment Initiation on SAE Rate:
Cross-Disease and Cross-Drug Validation

	Dependent Variable: Serious Adverse Event			
	Leave-cancer-out SAE risk		Leave-drug-out SAE risk	
	Model 2	Model 4	Model 2	Model 4
Post-period average	0.024	0.024	0.024	0.024
	(0.002)	(0.002)	(0.002)	(0.002)
Post-period risk effect	0.416	0.420	0.363	0.372
	(0.066)	(0.066)	(0.067)	(0.068)
1 SD higher SAE risk	0.007	0.007	0.006	0.006
	(0.001)	(0.001)	(0.001)	(0.001)
Calendar time	X	X	X	X
Time since diagnosis	X	X	X	X
Individual fixed effects		X		X
Observations	560,246	560,246	548,439	548,439
Unique patients	24,002	24,002	23,437	23,437

Notes: This table reports the treatment-effect estimates θ_0 and θ_1 from Equation 2 using alternative measures of baseline risk than the baseline analysis. Columns 1 and 2 use a LASSO risk estimate that excludes every patient with the same primary tumor site from the construction of the risk measure, testing for cross-disease validity of the risk estimate. Columns 3 and 4 use a LASSO risk estimate that excludes every patient whose cancer drug regimen includes any of the drugs prescribed to the index patient.

Table A13: Effect of Treatment Initiation on SAE Rate:
Broad Cohort with Treatment Initiation in Months 3-11

	Dependent Variable: Serious Adverse Event			
	Model 1	Model 2	Model 3	Model 4
Post Treatment Initiation	0.022	0.022	0.022	0.022
	(0.0009)	(0.0009)	(0.0009)	(0.0009)
Post × (SAE Risk - $\overline{\text{SAE Risk}}$)		0.446		0.462
		(0.0517)		(0.0518)
ΔY for 1 SD higher SAE risk		0.007		0.007
		(0.001)		(0.001)
Calendar time	X	X	X	X
Time since diagnosis	X	X	X	X
Individual fixed effects			X	X
Number of patients	30,589	30,589	30,589	30,589
Number of observations	597,916	597,916	597,916	597,916

Notes: This table reports the treatment-effect estimates θ_0 and θ_1 from Equation 2 using a broader cohort of patients than the baseline analysis. The broadened sample includes 30,589 unique patients and 597,916 patient-month observations spanning from 12 months before diagnosis until up to 2 months post-treatment initiation.

Table A14: Predicted SAE Risk by Time-to-Treatment Initiation

Months since diagnosis until treatment	Sample size	Mean predicted SAE risk
0	11,171	0.0395
1	30,241	0.0407
2	23,363	0.0377
3	12,509	0.0363
4	5,924	0.0358
5	3,444	0.0346
6	2,125	0.0340

Notes: The risk model summarized in Table 3 was applied to a subset of patients who initiated treatment between 0 and 6 months since diagnosis.

Table A15: Relationship between SAE Risk and Trial Participation

Percentile	Predicted SAE risk	Predicted SAE treatment effect	Predicted trial participation
10th	0.0144	0.0136	0.0081
25th	0.0213	0.0169	0.0073
50th	0.0328	0.0223	0.0058
75th	0.0474	0.0292	0.0039
90th	0.0618	0.0359	0.0021

Notes: This table reports the distribution of Predicted SAE risk, predicted SAE treatment effects, and trial participation in the Trial Participation Cohort. Predicted SAE treatment effects represent monthly estimates obtained using Model 2 coefficients from Table 4. Predicted trial participation obtained using the coefficient estimates from the logit model estimated in Table 5 Panel A Column 1.

Table A16: Normalized Relationship between SAE Risk and Trial Participation

	Dep. Variable: $1\{Trial\ Participant\}/Pr(Trial\ Participant|Disease\ state)$		
	Full sample	Advanced stage cancers	Early stage cancers
Panel A. Controlling for Disease Cohorts Only			
SAE risk	-22.887	-23.195	-22.784
	(2.729)	(3.131)	(3.489)
Panel B. Controlling for Age, Sex, Race, and Disease cohorts			
SAE risk	-17.929	-21.998	-16.336
	(2.803)	(3.103)	(3.641)
Mean trial participation	0.005	0.011	0.004
Sample size	157,715	38,934	118,781

Notes: This table reports coefficients from linear regressions where the outcome variable is Trial Participation divided by the probability of trial participation in the patient's disease state; this normalization will lead a proportional relationship to be expressed as additive effects in the linear regression model. The key independent variable of interest is predicted SAE risk. Panel A reports the coefficient estimate and standard error of the SAE risk variable in a linear regression controlling for 28 disease state fixed effects (cancer type × stage at diagnosis × treatment line × biomarkers). Panel B reports the results from a linear regression controlling also for age, age squared, sex, and race (White, Black, American Indian and Alaska Native, Asian and Pacific Islander, Other). Heteroskedastic robust standard errors are reported in parentheses.

Table A17: Relationship between Industry-Funded, Phase 3 Trial Participation and SAE Risk

	Dependent Variable: Participant in Industry-funded, Phase 3 Trial		
	Full sample	Advanced stage cancers	Early stage cancers
Panel A. Controlling for Disease Cohorts Only			
SAE risk	-27.311	-30.354	-22.205
	(3.613)	(4.676)	(5.541)
Percent change in odds from 1 s.d. higher SAE risk	-39.6%	-41.9%	-32.7%
	(4.03)	(4.86)	(6.65)
Panel B. Controlling for Age, Sex, Race, and Disease cohorts			
SAE risk	-22.523	-29.038	-10.583
	(3.722)	(4.811)	(5.433)
Percent change in odds from 1 s.d. higher SAE risk	-34.0%	-40.5%	-17.2%
	(4.53)	(5.12)	(8.02)
Mean trial participation	0.002	0.005	0.001
Sample size	157,715	38,934	118,781

Notes: This table reports coefficients from logistic regressions where the outcome variable is participation in industry-sponsored Phase 3 trials and the key independent variable of interest is predicted SAE risk, in the Trial Participation Sample. Panel A reports the coefficient estimate and standard error of the SAE risk variable in a logistic regression controlling for 28 disease state fixed effects (cancer type × stage at diagnosis × treatment line × biomarkers). Panel B reports the results from a logistic regression controlling also for age, age squared, sex, and race (White, Black, American Indian and Alaska Native, Asian and Pacific Islander, Other). Heteroskedastic robust standard errors are reported in parentheses.

Table A18: Calibration of Model: Does improving SAE representativeness improve net benefit representativeness?

	Monthly SAE TE ×3	**Monthly SAE TE ×6**
	Values of h:	
	-0.0488	-0.0244
Values of δ	*Max value of $\lvert B_\alpha \rvert / \lvert B_\gamma \rvert$, if $B_\alpha > 0$:*	
0.01	0.029	0.017
0.05	0.049	0.037
0.10	0.074	0.062
0.20	0.124	0.112
0.30	0.174	0.162
0.40	0.224	0.212

Notes: This table summarizes the calibration exercise reported in Section 6. We consider two alternative re-scalings of our monthly SAE TE results to match the annual cancer mortality risk variable. Column 1 assumes only three months of elevated SAE risk (since that was the post-period used in estimation) and multiplies our monthly estimate by 3. Column 2 assumes six months of elevated SAE risk. The top row reports the slope coefficient from a regression of treatment benefits (predicted mortality reduction) on treatment harms (predicted rate of induced SAE hospitalizations), estimated in the SAE Sample. If $B_\alpha <= 0$ so that under current enrollment patterns, trials overstate treatment benefits, then checking that $-h < \delta$ is sufficient to ensure that the proposed regulation would improve SAE representativeness. If $B_\alpha >= 0$ (trials understate treatment benefits), then we also require the condition reported in the bottom panel: i.e., that B_α is much smaller in magnitude than B_γ, with the maximum proportion depending on δ and reported in the bottom table.