Study Protocol

Communicating uncertainties associated with the benefits and risks of new cancer drugs

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Randomized pre-post survey to evaluate the effect of communicating uncertainties from different sources

Introduction

Many newer cancer drugs are approved before uncertainties with their underlying clinical trial evidence have been adequately studied, in turn making it difficult to accurately determine the drug's benefits and harms.[1] For example, nearly one-third of new cancer drugs are approved without comparative data versus existing treatments.[2] Fewer than half of cancer drugs demonstrate improvements on outcomes that matter most to patients (quality of life and overall survival), instead measuring unvalidated surrogate endpoints.[3,4] Other uncertainties with new cancer drugs stem from a lack of diversity of clinical trial participants,[5,6] and limited long-term data on the drug's effects.

Regulated information about prescription drugs rarely acknowledges these uncertainties, which limits the ability of patients and physicians to make informed and evidence-based decisions. In this study, we will examine the effect of communicating epistemic uncertainty associated with limitations in the clinical trial evidence supporting new cancer drugs. Cancer drugs are the single largest therapeutic category of new drug approvals,[7] and the frequency and magnitude of uncertainties associated with the evidence of these drugs at the time of approval are considerable and increasing. Relative to other drugs, cancer drugs are more likely to be supported by fewer late-phase clinical trials at the time of approval. They are also more likely to be approved on the basis of non-randomized single arm trials and unvalidated surrogate endpoints.[8]

However, prescription drug information rarely communicates uncertainties associated with the evidence of new drugs.[9] As a result, there can be substantial differences between patients' expectations and understanding of treatment, and evidence on the drug's benefits and harms.[10] Misperceptions are common among patients with metastatic cancer, who may mistake the palliative intent of treatment as being curative, and overestimate their likelihood of surviving longer.[11] Misunderstanding the evidence of a drug's benefits can also compromise patients' ability to make informed decisions. Patients may have preferred choices that would have preserved their quality of life, rather than being exposed to the physical, financial, and time toxicities of non-curative and non-life extending treatments.[12]

Objective

To evaluate the effect of using brief statements to communicate different sources of uncertainty about the benefits and harms of new cancer drugs on participants' decisions.

Randomization

We will conduct a randomized pre-post survey, evaluating the change in participants' decisions before and after being given information about a source of uncertainty with a new cancer drug's benefits and harms. By using a pre-post design, each group will serve as their own control and the randomization will ensure that participant characteristics are equally distributed. Participants will be randomized to 1 of 5 experimental conditions. Randomization will be done at the participant level, using the survey platform Qualtrics.

Participants
We will recruit a nationally representative sample of US adults to participate in this study. Eligible participants will be above 18 years of age and fluent in English. Participants will be recruited through CloudResearch, a market research company which engages with hundreds of research panel providers that use various methods for recruitment. Participants will be asked for informed consent before initiating the survey. No identifying information about participants will be asked or known by the study team, and CloudResearch will not have access to the participants' responses.

Intervention
In the pre-intervention phase, participants will be given information about a hypothetical new drug approved by the FDA for the treatment of non-small cell lung cancer. We based the information on adagrasib, which received accelerated approval in 2022 for the treatment of adults with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer who have received at least one prior systemic therapy. We then developed brief statements to communicate the most common sources of uncertainties with new cancer drugs cited in FDA approval decisions (**Table 1**): (1) single-arm trial designs,[13] (2) limited study populations (i.e., generalizability of clinical trial evidence),[14,15] and (3) limited study durations (i.e., long-term benefits and harms). We also included two additional uncertainties that are frequently mentioned in the scientific literature: (4) the use of unvalidated surrogate endpoints to support new cancer drug approvals,[16,17] and (5) uncertain treatment effect size (i.e., the magnitude of therapeutic benefit).[18]

Procedure
At the start of the survey, participants will be given a vignette describing a 38-year-old woman diagnosed with non-small cell lung cancer. The woman's doctor tells her about a new drug that was approved by the FDA for her disease and that is covered by her insurance. Participants will then be presented with a table summarizing the main benefits and harms of the drug, which was developed using the FDA's Drug Trials Snapshot for adagrasib.

In the pre-intervention phase, we will ask participants how likely they would be to take the drug if they were in Alex's position, and how certain they are that the drug will work. Participants will then be randomized to 1 of 5 statements about a source of uncertainty with the drug's evidence. The post-intervention questions will re-assess participants' decisions and perceptions of uncertainty, as well as their understanding of the uncertainty communicated in the statement.

Primary outcome
The co-primary outcomes of this study are changes in decision making and understanding. For decision making, we will measure the effect of communicating different sources of uncertainties on the change in participants' hypothetical decisions, measured as the pre-post difference in their decision to take the drug if they were diagnosed with non-small cell lung cancer. For understanding, we will evaluate whether participant are able to identify the source of uncertainty with the drug's evidence that they were randomized to.

Secondary outcomes
Participants' perception of uncertainty (how confident they are the drug will work for Alex).

Statistical analysis

We will compare the change in participants' decisions pre- and post-intervention using the McNemar's X^2 test for paired data. In adjusted analyses, we will use regression models to control for covariates.

Similar to previous studies that have communicated uncertainties with surrogate endpoints,[19,20] we assumed an approximate 10% absolute difference in participants decisions' pre- and post-intervention (60% vs 50%), which resulted in approximately 500 people per group. We plan to recruit 600 per group (3,000 in total) in case of dropouts or errors during survey completion.

We plan to exclude participants who complete the survey in 40% of the anticipated completion time, a conservative cutoff that is consistent with other studies.[21]

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Table: Statements communicating sources of uncertainties

Source of uncertainty	Statement about uncertainty
Single-arm trial	Because Zenova has not been compared to other treatments, it is unknown if Zenova is better, the same, or worse than other treatments for non-small cell lung cancer.
Limited study duration (Long-term benefits and harms)	Since patients given Zenova were followed for a short time, the longer-term benefits and harms of taking Zenova are unknown.
Limited study population (generalizability)	Zenova has not been studied in patients similar to Alex (patients with her race and ethnicity). It is unknown whether Zenova will work and what harms it will have for patients like her.
Unvalidated surrogate endpoint	Zenova has only been shown to shrink the size of tumors. It is unknown whether Zenova improves how patients feel or how long they live.
Treatment effect size (magnitude of therapeutic benefit)	It is unknown whether patients with non-small cell lung cancer will notice an improvement with Zenova.

Survey

Communicating Information About Prescription Drugs

Welcome. Thank you for your interest in this study.

About this study

Researchers are interested in how to better communicate information about prescription drugs to the public.

This study is being led by researchers at the London School of Economics and Political Science (UK) and Harvard Medical School (US). Funding was provided by Arnold Ventures and the LSE Phelan United States Centre.

The survey takes about 10 minutes to complete.

Consent
Participation in this survey is voluntary. The survey is anonymous – that means we will not record your name or any information that could connect you to your answers.

If you have any questions regarding this study, please contact the researcher, Avi Cherla, at a.j.cherla@lse.ac.uk. If you have any concerns regarding the conduct of this research, please contact the LSE research ethics managers via research.ethics@lse.ac.uk.

Instructions
Please try to answer all questions even if you are not completely sure about an answer. Once you complete a question, you will not be able to go back and change your answer.

By clicking the next button, you indicate that you:

1) Are 18 years or older
2) Live in the US
3) Are fluent in reading, writing, and speaking in English
4) Have read and understand the instructions
5) Consent to participating in the survey

Section A: Sources of prescription drug information

First, we want to learn about how you find information about prescription drugs.

1. When you are looking for information about prescription drugs, how often do you use each of the following sources? (Matrix grid response options: Never, rarely, sometimes, often)
    - Print media (for example, New York Times, Wall Street Journal)
    - Broadcast media (for example, CNN, Fox, NBC)
    - Social media (for example, Facebook, Twitter [X], Instagram)
    - Government website (for example, FDA, CDC)
    - Other health websites (for example, WebMD, Mayo Clinic)
    - Advertisements (TV, online, or print)
    - Family or friends
    - Physician, nurse, or other health professional

2. Do you trust that information about prescription drugs from these sources is correct? (matrix grid with sources from above)
    - Strongly disagree
    - Somewhat disagree
    - Somewhat agree
    - Strongly agree

3. Overall, how easy is it for you to find trustworthy information about prescription drugs?
    - Very difficult
    - Somewhat difficult
    - Somewhat easy
    - Very easy

Next, you will be presented with a scenario, followed by a series of questions relating to it. [stand-alone page]

Please read the following scenario about Alex.

Alex is 38 years old. A year ago, Alex was diagnosed with non-small cell lung cancer that had spread to other parts of her body. Since her diagnosis, Alex has tried 2 different treatments, but none have worked. Alex's doctor says that less than 10% of people in her situation live for more than 5 years.

Alex's doctor tells her that the US Food and Drug Administration (FDA) recently approved a new drug for patients like her who did not respond to other treatments. Her doctor wants to know if she would be interested in taking the drug. It would be covered by Alex's health insurance with no additional costs.

Here is the information Alex's doctor gave her to help her decide about the new drug. The source of this information was the US Food and Drug Administration (FDA).

Information about ZENOVA for non-small cell lung cancer	
ZENOVA is a prescription medicine used to treat adult patients with non-small cell lung cancer (NSCLC) that has an abnormal KRAS G12C gene mutation, is locally advanced or has spread to other parts of the body (metastatic) and has progressed on or after one prior treatment. The FDA approved ZENOVA based on evidence from 1 clinical trial in 112 patients.	
Benefits	**% of patients in trial**
Partial or complete shrinkage of tumors	**43%**
Complete shrinkage of tumors	1%
Partial shrinkage of tumors	42%
Harms	**% of patients in trial**
Serious harms (life threatening or requiring hospitalization)	**45%**
Pneumonia	17%
Hepatoxicity (liver damage)	10%
Common side effects	**98%**
Diarrhea	70%
Nausea	69%

Section D: Decision making (pre intervention)

4. Imagine you were Alex and diagnosed with non-small cell lung cancer. How likely are you to take the new drug, Zenova?
    - Very unlikely
    - Somewhat unlikely
    - Somewhat likely
    - Very likely

Section E: Perception of uncertainty (pre intervention)

5. How certain are you that Zenova will work for Alex?
    - Very uncertain
    - Somewhat uncertain
    - Somewhat certain
    - Very certain

Alex's doctor mentions that there was more information about Zenova available from the FDA. [separate page]

Here is the additional information, which is about uncertainties with Zenova:

[show uncertainty statement and drug table]

Section F: Decision making (post-intervention)

6. Considering this additional information, if you were Alex and diagnosed with non-small cell lung cancer, how likely are you now to take Zenova?
    - Very unlikely
    - Somewhat unlikely
    - Somewhat likely
    - Very likely

Section G: Perception of uncertainty (post-intervention)

7. Considering the additional information you learned about Zenova, how certain are you now that Zenova will work for Alex?
    - Very uncertain
    - Somewhat uncertain
    - Somewhat certain
    - Very certain

Section H: Understanding

8. Please rate your agreement with the following statements. (Matrix grid with 5 point scale for strongly disagree, disagree, etc.)
    - Zenova works better than other treatments for non-small cell lung cancer
    - Zenova's longer-term benefits and harms are well known
    - Zenova has been studied in patients that are similar to Alex (race and ethnicity)
    - Zenova improves how patients feel or how long they live
    - Zenova has a very large benefit for patients with non-small cell lung cancer

Section I: Perceived importance of knowing about uncertainty

9. Was the additional information about uncertainty with Zenova helpful to your decision?
    - Strongly disagree
    - Somewhat disagree
    - Somewhat agree
    - Strongly agree

10. Do you think that uncertainties about drug benefits and harms should always be communicated?
    - Strongly disagree
    - Somewhat disagree
    - Somewhat agree
    - Strongly agree

Imagine that your doctor prescribed you a new drug and there was some information about the drug that was still unknown. Which of these uncertainties do you think are important to know when deciding about taking a new drug?

11. Unknown whether the drug is better or worse than other treatments.
    1. Not at all important
    2. Somewhat unimportant
    3. Somewhat important
    4. Very important

12. Unknown what the long-term benefits and harms of the drug are.
    1. Not at all important
    2. Somewhat unimportant
    3. Somewhat important
    4. Very important

13. Unknown how well the drug works for someone of your age, of your race, or with your health conditions.
    1. Not at all important
    2. Somewhat unimportant
    3. Somewhat important
    4. Very important

14. Unknown whether the drug will help patients feel better or live longer.
    1. Not at all important
    2. Somewhat unimportant
    3. Somewhat important
    4. Very important

15. Unknown whether patients notice a difference with the drug (the benefits are too small to notice).

1. Not at all important
2. Somewhat unimportant
3. Somewhat important
4. Very important

Section J: Demographics

Finally, please tell us about yourself.

16. How old are you?
    - 18 to 24
    - 25 to 44
    - 45 to 64
    - 65 and older

17. What is your sex?
    - Male
    - Female
    - Other
    - Prefer not to say

18. What is your race and ethnicity?
    - White
    - Hispanic or Latino
    - African American or Black
    - American Indian or Alaska Native
    - Asian
    - Other

19. What is the highest level of education that you completed?
    - Less than high school
    - High school or equivalent
    - College or undergraduate degree
    - Graduate degree and higher

20. What is your approximate yearly income?
    - Less than $25,000
    - $25,000 to $49,999
    - $50,000 to $74,999
    - $75,000 to $99,999
    - More than $100,000

21. Have you, a close friend, or immediate family member (i.e. your partner, parents, siblings, or children) ever been diagnosed with cancer? (Select as many that apply).
    - I have been diagnosed (currently, or in the past)

- An immediate family member has been diagnosed
- A close friend has been diagnosed
- To my knowledge, none of my close friends or family, or myself, has been diagnosed with cancer

22. How would you describe your political views?
    - Liberal
    - Slightly liberal
    - Moderate
    - Slightly conservative
    - Conservative
    - Prefer not to say

23. Would you describe yourself as generally optimistic or pessimistic?
    - Pessimistic
    - Somewhat pessimistic
    - Neither pessimistic or optimistic
    - Somewhat optimistic
    - Optimistic

24. How often do you need someone to help you understand instructions or other written material from your doctor or pharmacy about prescription drugs?
    - Never
    - Rarely
    - Sometimes
    - Often
    - Always