Study Protocol

Communicating uncertainties associated with the benefits and risks of new cancer drugs: two national randomized surveys

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Objective
To evaluate the effect of communicating multiple sources of uncertainty about the benefits and harms of new drugs on participants' decisions.

Study design and randomization
In this randomized controlled trial using a pre-post study design,[1] participants will be randomized with equal allocation to 1 of 5 groups. The control group will receive information about a new cancer drug's benefits and harms; the intervention groups will also be given brief statements about sources of uncertainties with the drug's evidence (1, 2, 3, or 4 sources of uncertainties).

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. Eligible participants were not allowed to have participated in the earlier survey, which we verified through unique participant identifiers assigned to each participant from the survey company.

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
We developed brief statements to communicate the most common sources of uncertainties with new cancer drugs cited in FDA approval decisions and the scientific literature.[2] In the first study, we evaluated the effect of communicating different individual sources of uncertainties on participants' hypothetical decisions. In this second trial, we will evaluate the additive effect of communicating multiple sources of uncertainties.

Given the combinations of uncertainties that could have been tested in this trial, we will focus on the sources of uncertainties that had the largest effects on participants' decisions in the first trial. Therefore, participants randomized to receive 2 sources of uncertainties received the 2 that had the largest effects in the first trial, and so forth. **Table 1** presents the combinations of statements that will be tested in this trial.

Procedure
At the start of the survey, participants will be given a vignette describing a 38-year-old woman that was recently 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 about how likely they would be to take the drug if they were in Alex's position, how certain they are that the drug will work, and how worried they would feel about taking the drug. We will also assess their understanding of the drug's benefits and risks. Participants will then be randomized to 0, 1, 2, 3 or 4 statements about sources of uncertainty with the drug's evidence. The post-intervention questions will re-assess decision-making, perceptions, emotions, and understanding, as well ask participants about their trust in the information that they were given, and the FDA.

Primary outcome
The primary outcome is the pre-post change in participants decisions to take the new cancer drug in each experimental condition relative to the control group. Decision-making was

measured using a 4-point Likert scale: very likely, somewhat likely, somewhat unlikely, and very unlikely. For the primary analysis we will categorize participant responses as binary and focus on participants who changed their decisions from likely (pre-intervention) to unlikely to take the drug (post-intervention).

Secondary outcomes

Secondary outcomes will compare participants' understanding of uncertainties, perceptions, and emotions after learning about a source of uncertainty relative to the difference in the control group. We will also assess trust associated with communicating uncertainty.[3]

For understanding (measured on a 4-point Likert scale: strongly disagree to strongly agree), we will compare the percentage of participants who improved their understanding of the drug after being randomized to a source of uncertainty.[1] For perceptions (measured on a 4-point Likert scale: very uncertain to very certain), we will compare the percentage of participants who were less certain that the drug would work well after learning about a source of uncertainty, and for emotions (measured on a 4-point Likert scale: extremely worried to not worried at all), we will compare the percentage of participants that were more worried about taking the drug after learning about a source of uncertainty.[3–6] To assess trust, we will ask participants about their perceived trust in the information and the source of the information (measured on a 4-point Likert scale: not at all trustworthy to very trustworthy),[7,8] and whether learning about uncertainties made them more or less trusting in the FDA (measured on a 4-point Likert scale: less trusting to more trusting).

Statistical analysis

For the primary analysis comparing differences between the experimental conditions and the control group, we will use generalized estimating equations. To compare differences between groups in trust, which was only measured post-intervention, we will use X^2 tests. As a sensitivity analysis we will use the X^2 test (or Fischer's exact test as appropriate) to evaluate the percentage difference between groups in participants who were likely to take the drug post-intervention. To provide comparable estimates of the within group differences (changes from pre to post responses) for the trial, we will use McNemar's X^2 test for paired data.

We powered the trial to detect a between group difference of 10% (65% post intervention for control vs 55% post intervention for the experimental groups) based on findings from the first trial, with 90% power and a two-sided alpha of 0.05. We aimed to recruit 600 participants per group in case of dropouts or errors during survey completion.

We plan to exclude participants who complete the survey in less than 150 seconds, a conservative cutoff that is consistent with other studies.[9] We will also exclude participants who do not complete the survey and who provide straight-line responses.

References

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Table 1: Statements communicating multiple sources of uncertainties

Source of uncertainty	Statements communicating uncertainties
Small magnitude of effect	• It is unknown whether patients with non-small cell lung cancer will notice an improvement with Zenova.
Small magnitude of effect Limited study population	• It is unknown whether patients with non-small cell lung cancer will notice an improvement with Zenova. • 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.
Small magnitude of effect Limited study population Unvalidated surrogate endpoint	• It is unknown whether patients with non-small cell lung cancer will notice an improvement with Zenova. • 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. • 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.
Small magnitude of effect Limited study population Unvalidated surrogate endpoint Limited study duration	• It is unknown whether patients with non-small cell lung cancer will notice an improvement with Zenova. • 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. • 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. • Since patients given Zenova were followed for a short time, the longer-term benefits and harms of taking Zenova are unknown.

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.

The survey takes about 10 minutes to complete.

Consent
Completion of 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%

PRE-INTERVENTION QUESTIONS

Section B: Decision making

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

Section C: Perception of certainty

5. How certain are you that Zenova will work for Alex?
    1. Very uncertain
    2. Somewhat uncertain
    3. Somewhat certain
    4. Very certain

Section D: Emotions

6. If you were Alex, how worried would you feel about taking Zenova?
    1. Extremely worried
    2. Slightly worried
    3. Not very worried
    4. Not worried at all

Section E: Understanding

7. Please rate your agreement with the following statements. (4-point scale: strongly disagree, somewhat disagree, somewhat agree…)
    - 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 noticeable improvement for patients

POST-INTERVENTION QUESTIONS

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

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

Section G: Perception of certainty

9. Considering this additional information, how certain are you now that Zenova will work for Alex?
    1. Very uncertain
    2. Somewhat uncertain
    3. Somewhat certain
    4. Very certain

Section H: Emotions

10. If you were Alex, how worried would you now feel about taking Zenova?
    5. Extremely worried
    6. Slightly worried
    7. Not very worried
    8. Not worried at all

Section I: Understanding

11. Please rate your agreement with the following statements again. (4-point scale)
    - 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 noticeable improvement for patients with non-small cell lung cancer

Section J: Trust

12. To what extent do you think the information about Zenova is trustworthy?
    1. Not at all trustworthy
    2. Somewhat untrustworthy
    3. Somewhat trustworthy
    4. Very trustworthy

13. To what extent do you think the FDA, who approved Zenova and produced this information, is trustworthy?
    1. Not at all trustworthy
    2. Somewhat untrustworthy
    3. Somewhat trustworthy
    4. Very trustworthy

14. Did having additional information about Zenova make you more or less trusting of the FDA?
    1. Less trusting
    2. Somewhat less trusting
    3. Somewhat more trusting
    4. More trusting

Section K: Perceived importance of knowing about uncertainty

15. Was the additional information about uncertainty with Zenova helpful to your decision?
    1. Strongly disagree
    2. Somewhat disagree
    3. Somewhat agree
    4. Strongly agree

16. Do you think that uncertainties about drug benefits and harms should always be communicated?
    1. Strongly disagree
    2. Somewhat disagree
    3. Somewhat agree
    4. 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 the following do you think are important to know when deciding about taking a new drug?

17. 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

18. 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

19. 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

20. 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 L: Demographics

Finally, please tell us about yourself.

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

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

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

24. 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

25. 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

26. 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

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

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

29. 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