PROTOCOL VERSION 11, 08/06/2023
LEVELS OF EVIDENCE: A VIGNETTE STUDY

OBJECTIVE

To determine which study type clinicians would preferably plan to answer a therapeutic oncology question lacking evidence.

METHODS

Clinical situation

We will start with the following therapeutic strategy situation, which occurs frequently in oncology:

*For a common metastatic cancer **X**, treatment **A** is the usual first-line treatment. Treatment **B** is also prescribed in clinical practice but has never been compared to treatment **A.** We would like to compare treatment **A** to treatment **B**.* The difference in effect is expected to be moderate.

Study rationale

The ideal scenario for answering this question with high quality and strong evidence would be a fast access to results from a large randomized controlled trial that would be funded and achieve planned recruitment. We know from experience that this is unlikely. Indeed, in oncology, therapeutic guideline recommendations are rarely supported by high levels of evidence as randomized controlled trials can be difficult to conduct with long delays before the availability of results [1]. Furthermore, a growing body of evidence from observational studies is providing fast access to results and a better reflection of real-world heterogeneity. However, these observational studies can be subject to bias and confounding which impact the quality of the evidence. Target trial emulation [2] is a new method which uses observational data to mimic the design features of a hypothetical pragmatic randomized trial (i.e. the target trial). It requires adjustment of confounding factors via matching or stratification or other methods. This method reduces the risk of bias found in simpler observational analyses.
With this in mind, we would like to know which study type clinicians would preferably plan to answer our therapeutic question considering study characteristics, the inherent level of evidence and the anticipated delay before the availability of final results.

Study design

We will perform a vignette-based inquiry among clinicians to assess their preferences regarding different study types which could be planned to answer our predefined clinical question. This study will take place from June 2023 to September 2023.

Vignettes

Development of the vignettes

Vignettes will be case scenarios of potential studies planned to answer our predefined question. We will propose six studies, three randomized controlled trials and three observational studies, each defined using the following key features:
-Study characteristics: design, setting, eligibility criteria, main outcome, methodology, sample size or size of available data source
-Probability of the study succeeding (funding, recruitment and access to data).
-Anticipated delay from the time the study starts to the availability of final study results.

To select these features, we searched published literature. Regarding randomized controlled trials, previously published meta-epidemiological studies showed that trial characteristics such as blinding [3, 4], single versus multicenter setting [5], age (eligibility criteria) [6] and sample size [5] were associated with treatment effects.
Many challenges regarding the quality of observational evidence, and interpretation of treatment effects in observational studies, have already been identified in the litterature, although a validated framework for quality is currently missing [7, 8]. In this context we will use the same study features for both randomized trials and observational studies, except for "sample size" which will be changed for "size of available data source".
Finally, for all six potential studies (i.e. vignettes), we will consider that the methodology and statistical analysis would follow current best practice standards and that target trial emulation and matching would be performed for the three observational studies [2].

The final selection of features for the potential studies and their content will be completed after consensus among expert methodologists (P.R., I.B., R.P., T.N.). The final design of all six vignettes will be reviewed and validated by all authors.

Data collection and outcome

This vignette-based enquiry will be constructed in two parts.

For the first part, all six vignettes will be compared in a pairwise manner, leading to 15 possible comparisons. To avoid bias related to the presentation of the scale, the studies will be randomly reported as study 1 or study 2. Therefore, there will be 30 possible combinations (i.e. 2 possible combinations for each comparison, with studies reversed).
We will evaluate clinicians' preferences regarding which type of study should be planned to answer the therapeutic question. Each participant will take on the role of a study investigator and will randomly assess 5 comparisons by responding to one question per comparison. For each comparison there will be only one answer possible using a Likert scale from -5 to 5 with no 0 (strongly favoring study 1 or study 2). The question asked for each comparison will be:

"If only one study could be planned, which study would you support?"

The second part will only be available after participants finish assessing the 5 comparisons. They will not be able to go back and change their answers. Summary results of a recently published study on trial emulation [9] will be shown, and we will assess if these results make them reconsider their previous answers to the survey. The question will be:

Considering these recent findings, would you change your previous answers to this survey?

Only one response will be possible using a Likert scale with 3 possible answers: Yes/No/No opinion.

Participants

We will recruit a nonprobability sample of international clinicians to answer the survey. Participants will receive an email and will be directed to the study website for survey completion if they agree to participate. The link to the website is the following:

https://clinicalepidemio.fr/evidence/

In the online survey, participants will need to acknowledge a few demographic points about: their profile (methodologist, clinician +/- methodologist); their experience as a principal investigator with randomized controlled trials, observational studies and emulated trials; their years of expertise; their country and their field of expertise in oncology. The survey will be anonymized.
Each participant will assess 5 comparisons in the first part, and answer one question in the second part.

Random assignment

A random assignment sequence of the 30 combinations will be generated by the statistician. Once a participant completes the demographic information, he/she will then be randomly assigned one of the 30 available combinations according to the randomization list, and so on until 5 randomly assigned comparisons have been assessed. No participant will come across the same comparison twice (i.e. no participant will receive a comparison which they have already encountered in a reversed order).

Statistical analysis

Participants' characteristics will be reported as number and percentage for categorical variables and as mean and standard deviation, median and interquartile range for continuous variables.

Then, for the first part:

We will do an overall **ranking** of the 6 studies. For each of the 6 studies, mean preference scores and their standard deviations will be calculated, a higher score representing the preferred study.
Agreement between clinicians will be assessed with intraclass correlation coefficients and 95% confidence intervals.
To assess the **association** between participant's demographic characteristics and their answers, we will perform 6 mixed linear regression models (one for each vignette compared with the 5 others) with random effects at the participant and at the comparison levels.

For the second part:

We will assess the percentage for each response on the Likert scale.

Data will be analyzed with R version 4.2.1. Statistical significance will be set at $P < .05$, and all tests will be 2-tailed. The unit of analysis will be the comparison assessment. All participants who will assess at least one comparison will be included in the analyses.

References

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