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# Interpretation of health news items reported with or without spin: A prospective meta-analysis of 16 randomized controlled trials

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# ABSTRACT

**Introduction:** We aim to compare the interpretation of health news items reported with or without spin. "Spin" is defined as a misrepresentation of study results, regardless of motive (intentionally or unintentionally) that overemphasizes the beneficial effects of the intervention and overstates safety compared to that shown by the results.

**Methods and analysis:** We have planned a series of 16 RCTs to perform a prospective meta-analysis. We will select a sample of health news items reporting the results of 4 types of study designs, evaluating the effect of pharmacologic treatment and containing the highest amount of spin in the headline and text. News items reporting 4 types of studies will be included: 1) pre-clinical studies, 2) phase I/II (non-randomized) trials, 3) randomized controlled trials (RCTs), 4) observational studies. We will rewrite the selected news items and remove the spin. The original news and rewritten news will be appraised by 4 types of populations: 1) French-speaking patients, 2) French-speaking general public, 3) English-speaking patients, and 4) English-speaking general public. Each RCT will explore the interpretation of news items reporting one of the 4 study designs by each type of population and will include a sample size of 300 participants. The primary outcome will be participants' interpretation of the benefit of treatment after reading the news items: (*What do you think is the probability that treatment X would be beneficial to patients? (scale, 0 [very unlikely] to 10 [very likely])*.
This study will evaluate the impact of spin on the interpretation of health news reporting results of studies by patients and the general public.

**Ethics and dissemination:** This study has obtained ethics approval from the Institutional Review Board of INSERM, (registration No IRB00003888). The description of all the steps and the results of this prospective meta-analysis will be available online.

**Registration number:** CRD42017058941

## Strengths and limitations of this study

- This will be the first prospective meta-analysis of randomized controlled trials for interpretation of health news items reporting the results of studies with or without spin.
- It will address the impact of spin on the interpretation of health news by patients and the general public.
- The involvement of patients and the public may help to improve the reporting of medical research in health news.
- News stories are only one way that the public hears news about health.
- Logistically, the recruitment of large number of participants at the same time may be a challenge, but to manage this, participants will be recruited separately for each trial.

# INTRODUCTION

Health news is an important way to communicate updates about medical research to the public. News items reporting the results of medical research attract a large audience [1]. However, the quality of reporting in health news is uneven. The merits of a wide range of treatments and tests are overplayed, and harms are underplayed [2]. Several studies have shown the presence of spin (i.e., distorted presentation of study results) in health news [3-10]. Distorted facts can be misleading and can affect the behaviour of physicians, healthcare providers and patients [1 11 12]. However, little research has assessed whether spin can affect readers' interpretation [13]. To our knowledge, no work has assessed that news items reported with spin can influence readers' interpretations.

Our hypothesis is that spin can influence the reader's interpretation of health news items. We aim to compare the interpretation of health news items reported with or without spin. We will focus on news items reporting studies evaluating the effect of a pharmacological treatment, containing the largest amount of spin in the headline and text, and receiving high levels of public attention online.

# METHODS

## Definition of "spin"

We define "spin" as a misrepresentation of study results, regardless of motive (intentionally or unintentionally) that overemphasizes the beneficial effects of the intervention and overstates safety compared to that shown by the results [14].

## Study design

We have planned a series of 16 randomized controlled trials (RCTs) to perform a prospective meta-analysis (MA), and a comparing the interpretation of health news items reported with or without spin. Each RCT will explore the interpretation of news items reporting one of 4 study designs: 1) pre-clinical studies, 2) phase I/II trials (non-randomized), 3) RCTs, and 4) observational studies. The news items reporting each study design will be assessed by 4 different targeted populations: 1) French-speaking patients, 2) French-speaking general public, 3) English-speaking patients, and 4) English-speaking general public. Each RCT will be a parallel group with two-arms. In each RCT, participants will be randomly assigned to appraise health news items reported with or without spin *(see figure 1)*.

The planning, implementation, analysis and writing of this protocol will follow the SPIRIT [15] and PRISMA-P [16] guidelines. This study has obtained ethics approval from the Institutional Review Board of INSERM, (registration No IRB00003888), and the protocol is registered at PROSPERO website (CRD42017058941).

## News items with and without spin

### *Selection of news items with spin*

News items reporting studies evaluating a pharmacologic treatment that received a great deal of public attention online and contained a large amount of spin in the headline and text will be selected from a sample of news items retrieved from Altmetric Explorer.

### *Search strategy*

We will search for articles on "PubMed" using the following search strategy: field ((Randomized controlled trial[Publication Type] OR Observational study[Publication Type]) OR Meta-analysis[Publication Type]) OR Randomized[Title/Abstract]) OR controlled[Title/Abstract]) OR trial[Title/Abstract]) OR cross-sectional[Title/Abstract]) OR case-control[Title/Abstract]) OR cohort[Title/Abstract]) OR Meta-analysis[Title/Abstract]) OR systematic review[Title/Abstract]) AND (has abstract [text] AND ("2014/01/01"[PDAT] : "2014/06/30"[PDAT])). The publication period will be restricted to the first 6 months of 2014 to minimize the risk of recall bias among study participants.

To retrieve relevant news coverage of these articles, we will apply the "PubMed search details" on "Altmetric Explorer". The Web application Altmetric Explorer provides access to all sources where the published study is mentioned online in the mass media and sorts the items according to the Altmetric score [17]. The Altmetric score is one way to quantify the public attention an article received in online news outlets, blogs and social media (https://www.altmetric.com/) (a high Altmetric score = high public attention).

***Screening process***

Screening will be performed in two steps: first, one researcher will systematically screen the retrieved Altmetric Explorer citations, which will be sorted from the highest to the lowest Altmetric score (i.e., highest to lowest amount of public attention), and will identify studies evaluating the effect of a pharmacological treatment, regardless of study design and study population (including human and animal/laboratory). For each study fulfilling eligibility criteria, the researcher will retrieve 1) the published article and 2) all related online news items available at Altmetric Explorer.

Second, the researcher will identify the news item with spin in the headline and text by using a standard scheme of spin [10 18]. When several news items have spin in the headline, the researcher will select the news item with the most spin in the text. We will include news items reported by general or medical news outlets or lay press whose target consumers are the general population.

As a quality procedure, a second researcher will confirm the eligibility of all included studies and screen 10% of the excluded studies.

The screening process will be performed sequentially, the studies being sorted from the highest to the lowest Altmetric score (i.e., highest to lowest public attention). We will include the first 40 studies fulfilling the eligibility criteria and relevant 40 news items containing the most spin in the headline and text: 10 reporting pre-clinical studies, 10 reporting phase I/II non-randomized trials, 10 news items reporting RCTs and 10 reporting observational studies.

***Identification and description of spin***

We will identify the spin in the headlines and text of selected news items and will classify them according to following 3 categories of spin — misleading reporting, misleading interpretation and misleading extrapolation — that were previously developed [10].

***Misleading reporting*** is defined as incomplete or inadequate reporting of any important information in the context of the research that could be misleading for the reader. This category includes 1) misleading reporting of study design; 2) not reporting study population (if an animal study); 3) selective reporting of outcomes favoring the beneficial effect of the treatment (e.g., statistically significant results for efficacy outcomes or statistically non-significant results for safety outcomes); 4) not reporting adverse events; 5) linguistic spin (i.e., any word or expression emphasizing the beneficial effect of the treatment [19]; 6) not reporting study limitations; 7) not reporting any caution about study design and results, and 8) any other type of misleading reporting not classified under the above section.

***Misleading interpretation*** is defined as an interpretation of the study results in news stories that is not consistent with the results reported in the scientific articles and overestimating the beneficial effect of the treatment. This category includes claiming 1) a beneficial effect of the treatment despite statistically non-significant results; 2) an equivalent effect of the treatment for statistically non-significant results in superiority RCTs; 3) that the treatment is safe for statistically non-significant results despite a lack of power; 4) safety of the treatment despite adverse events reported in the scientific articles; 5) a causal effect (i.e., implies a cause-and-effect relationship between the intervention being assessed and the outcome of interest [20]) despite a non-randomized study design; 6) a beneficial effect of the treatment despite a small

sample size; and 7) a beneficial effect despite lack of a comparator as well as 8) focus on p-value instead of clinical importance; 9) interpretation of relative risk as absolute risk; and 10) any other type of misleading interpretation not otherwise classified.

***Misleading extrapolation*** is defined as overgeneralization of study results in news stories to different populations, interventions or outcomes that were not assessed in the study. This category includes extrapolating 1) animal study results to human application; 2) preliminary study results to clinical application; 3) the effect of study outcomes to other outcomes for the disease; 4) the beneficial effect of the study intervention to a different intervention (e.g., broccoli, which contains sulphoraphane, was claimed as beneficial by health news items, but the study evaluated the benefit of a sulphoraphane compound only); and 5) from the study participants to a larger or different population as well as 6) inappropriate implications for clinical or daily use (i.e., an improper recommendation or advice to use the intervention in clinical practice or daily use not supported by study results); and 7) any other types of extrapolation not otherwise classified.

All other spin that could not be classified with this scheme will be systematically recorded and secondarily classified.

## Construction of news without spin

### *Format of the news items*

Our aim is to keep the same context and format of the original news item and conceal the names of pharmacological treatments, authors and funders to avoid evaluation bias. Consequently, to rewrite the news items we will:

1. Keep the same context and structure
2. Create hypothetical names of reported pharmacological treatments
3. Conceal the names of study authors and experts by using different names selected based on the origin of the name from an online list of names including all countries of the world (http://www.studentsoftheworld.info/penpals/stats.php3?Pays) to keep the news content natural.
4. Keep the name of the research institute/university/hospital where the study was conducted.
5. Replace the name of the funding source with standardized terms for profit or non-profit funding organizations.
6. Delete the name of the online news outlet, date the news story was published online, name of the journalist who wrote the news with spin, name of the medical journal in which the study was published, reference to the original article and trial registration number or name (if reported).

### *Guidelines to remove spin in the news items*

To construct health news stories without spin, we will delete the spin identified in the headline and text and will add some caution, depending on context. The guidelines used to remove the spin are described in Table 1. The guidelines to add caution are in Table 2.

One researcher (RH) will identify and remove the spin in each news item selected (in the headline and text) and will rewrite the news story without spin, according to the guidelines described in Tables 1 and 2. Two researchers (IB) and (AY) will check the rewritten news items. Finally, a sample of the rewritten news stories will be checked by a researcher working in the field of medical journalism (IO). Appendix 1 provides an example of a news item reported with and without spin. Our sample of news will contain 80 news items [40 original news items (with spin) and 40 rewritten news items (without spin)].

## Translation of the news items reported with and without spin

All news items will be translated into French language to be used in RCTs involving French-speaking participants. One French native speaker researcher (AY) will validate the French translation of news items. Further, a French medical journalist will also validate the French translated news items.

## Population

Each RCT will target one of the four following study populations:

1. French-speaking patients

2. French-speaking general public

3. English-speaking patients

4. English-speaking general public

### Eligibility criteria

We will enroll participants older than 30 years.

### Recruitment strategy

To recruit participants, we will contact online communities of patients, patients' associations, popular health forums, and investigators of e-cohorts. We will also use the online platform (www.findparticipants.com) which enables access to thousands of interested participants to participate in research studies worldwide. We will also advertise the study in hospitals and GP practices.

Each participant will provide an online informed consent at the time of enrollment.

We will send participants an invitation by email (appendix 2). If respondents agree to participate in the survey, an Internet link included in the invitation email will give them access to information regarding the study and a screening question asking them whether they are willing to participate in the study. If they answer yes, respondents will be randomly assigned to read 1 news item with spin or one news item without spin.

Invitation emails will be sent in waves until the planned number of participants log on and complete the assessment. A maximum of two reminders will be sent to participants.

## Interventions

We will compare the interpretation of "health news items" reported with spin (original news = active comparator) or without spin (rewritten news = experimental group).

## Random assignment

A random assignment sequence will be computer-generated by a statistician by using blocks of 10 (i.e., number of news items selected x 2) for each study design type. The list will not be disclosed to investigators. Allocation concealment will be assured by the use of a computerized random-assignment system. After randomization, participants will be asked to complete a questionnaire. Participants who log on and do not evaluate the news will be excluded and the news item will be automatically allocated to another participant.

## Blinding

Blinding of participants is not possible, but to minimize bias, participants will be blinded to the study hypothesis. All participants will be informed that they are participating in a survey about the interpretation of news reporting medical research that evaluates treatments. They will not be informed about the objectives and hypothesis of the study.

After the completion of study, each participant will be told about the study objectives, hypothesis and results.

## Study outcomes

*Our primary outcome* will be participants' interpretation of the benefit of the treatment measured on a scale from 0 to10.

1. *What do you think is the probability that treatment X would be beneficial to patients? (scale, 0 [very unlikely] to 10 [very likely])*

*Secondary outcomes* are as follows:

2. *What do you think is the size of the potential benefit for patients? (scale, [none, small, moderate or large])*
3. *How safe do you think that treatment X would be for patients? (scale, 0 [very unlikely] to 10 [very likely])*
4. *Do you think this treatment should be offered to patients in the short term? (scale, 0 [very unlikely] to 10 [very likely])*
5. *Do you think this treatment will make a difference in the existing clinical practice? (scale, 0 [absolutely no] to 10 [absolutely yes])*

## Sample size

Each participant will read a news item with or without spin. We want to assess a mean difference of 1.0 for the primary outcome between groups on a 0-10 scale, with a standard deviation of 2.5 [13]. For each RCT, a sample of 266 assessments of news items will be needed to detect an effect size of 0.4 with a power of 90% and α risk of 5% for each RCT. Each news item will be read the same number of times (balanced design) and we will to take into account clustering due to the fact that a news items will be read many times. To achieve this, we will use a sample size

of 300 participants (150 in each group) in each RCT (i.e., an inflation factor of about 1.1). Therefore, each news item will be assessed 15 times in each group (10 news items with or without spin for 150 participants) for each RCT.

### Statistical analysis

The statistical analysis will be undertaken by a statistician who will use R v2.15.1 (R foundation for Statistical Computing, Vienna, Austria) at the Center for Clinical Epidemiology, Paris, France. All outcomes will be quantitative and the number of participants and news items will be balanced in each group. For each RCT, the following analysis will be done: The differences between groups will be analyzed by using a linear mixed model with a fixed group effect and random group effect and news items–group interaction effects. Random effects will allow us to account for the following 2 levels of clustering: within-group clustering as a result of the news (each news item will be assessed 15 times in each group) and between-group clustering (pairing between the news used in the 2 arms of the trial). Inferences will be based on the restricted maximum likelihood. This model will compare the mean difference between 2 arms for each trial. For primary and secondary outcomes, we will estimate the difference between means with 95% confidence intervals (CIs). $P$ <0.05 will be considered statistically significant.

Finally, after analyzing each RCT separately, a prospective meta-analysis will be done to summarize intervention effects. The mean difference with 95% CIs will be estimated by using a random-effects model based on the DerSimonian-Laird method. Forest plots will be created for visual interpretation of results. The heterogeneity will be assessed by $X^2$ test *($P$ <0.05)* and degree of heterogeneity by the $I^2$ statistic *(>75%)* to assess statistical significance (Higgins JPT et al, 2014). We will also assess the variance ($\tau^2$) between trials.

## STUDY DURATION

The total duration of this study will be 24 months. Expected period of inclusion of participants will also be 24 months and the duration of participation per participant/patient will be 1 hour. The anticipated start date of trials will be June, 2017.

# MODIFICATIONS MADE IN THE PROTOCOL SUBMITTED TO ETHICAL COMMITTEE

We made following changes in the protocol submitted to the ethical committee:

**Rewriting news items**

- Word count: The condition to keep the word count of ±20% from original news to rewritten news items is deleted.
- Concealment: The name of the research institute/university/hospital where the study was conducted will be kept in the rewritten news items.
- Guidelines to remove spin: We will also report the caution or recommendation by study authors, reported in the related article when available.

**Survey questionnaire**

- We merged two questions related to demographic information into one: How often do you read news items? Never/sometimes (once per month)/often(once per week)/daily

**Guidelines**

- We report SPIRIT and PRISMA-P guidelines to follow for protocols of clinical trials and meta-analysis respectively.

# DISCUSSION

To best of our knowledge, we present the first prospective meta-analysis of randomized controlled trials for interpretation of health news items reporting the results of studies with or without spin.

We have designed 16 randomized controlled trials which will focus on interpretation of news items reporting results of 4 types of study designs: 1) pre-clinical studies, 2) phase I/II trials (non-randomized), 3) RCTs, and 4) observational studies. There will be 80 news items reporting these study designs (20 new items / study design: 10 original news items with spin + 10 rewritten news items without spin). Each RCT will target one of the 4 types of populations: 1) French-speaking patients, 2) French-speaking general public, 3) English-speaking patients, and 4) English-speaking general public. In total, 4800 participants will be involved in 16 planned RCTs (300 participants/ RCT). Once the planned RCTs are completed, then the results of different RCTs will be included to perform a meta-analysis.

The concept of prospective meta-analysis allows us to compare the interpretation of health news stories reporting results of studies with or without spin by different types of populations. This new form of synthesis of evidence answers the question of whether spin can influence patients' and the publics' interpretation of health news.

We will document all practical issues and difficulties encountered to demonstrate that this type of synthesis of evidence is feasible. We are aware of some challenges, such as recruitment of participants. Logistically, the recruitment of large number of participants at the same time may be a challenge, but to manage this, participants will be recruited separately for each trial.

# EXPECTED RESULTS

This study will evaluate the impact of spin on patients' and the public's interpretation of news items reporting results of studies.

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**Contributors**
RH: Helped with conception of study design, selecting news items, rewriting news items and wrote the draft of the protocol, AY: Helping with validation of rewritten the news items and French translation of selected news items, PR: Conception of study design, GB: Helped to write the statistical analysis, IO: Helped with survey questionnaire and validation of rewritten news items, GS: Helped with survey questionnaire, IB: Conception of study design, validating rewritten news items, and helped to write the draft of the protocol.
All authors read and approved the final protocol.

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**Competing interests**
None declared

**Data sharing statement**
This article is the protocol of a prospective meta-analysis. The authors plan to report transparently all the planned trials and will provide open access to all extracted data for each trial.

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**Figure 1: Series of 16 RCTs that will be included in the prospective meta-analysis**

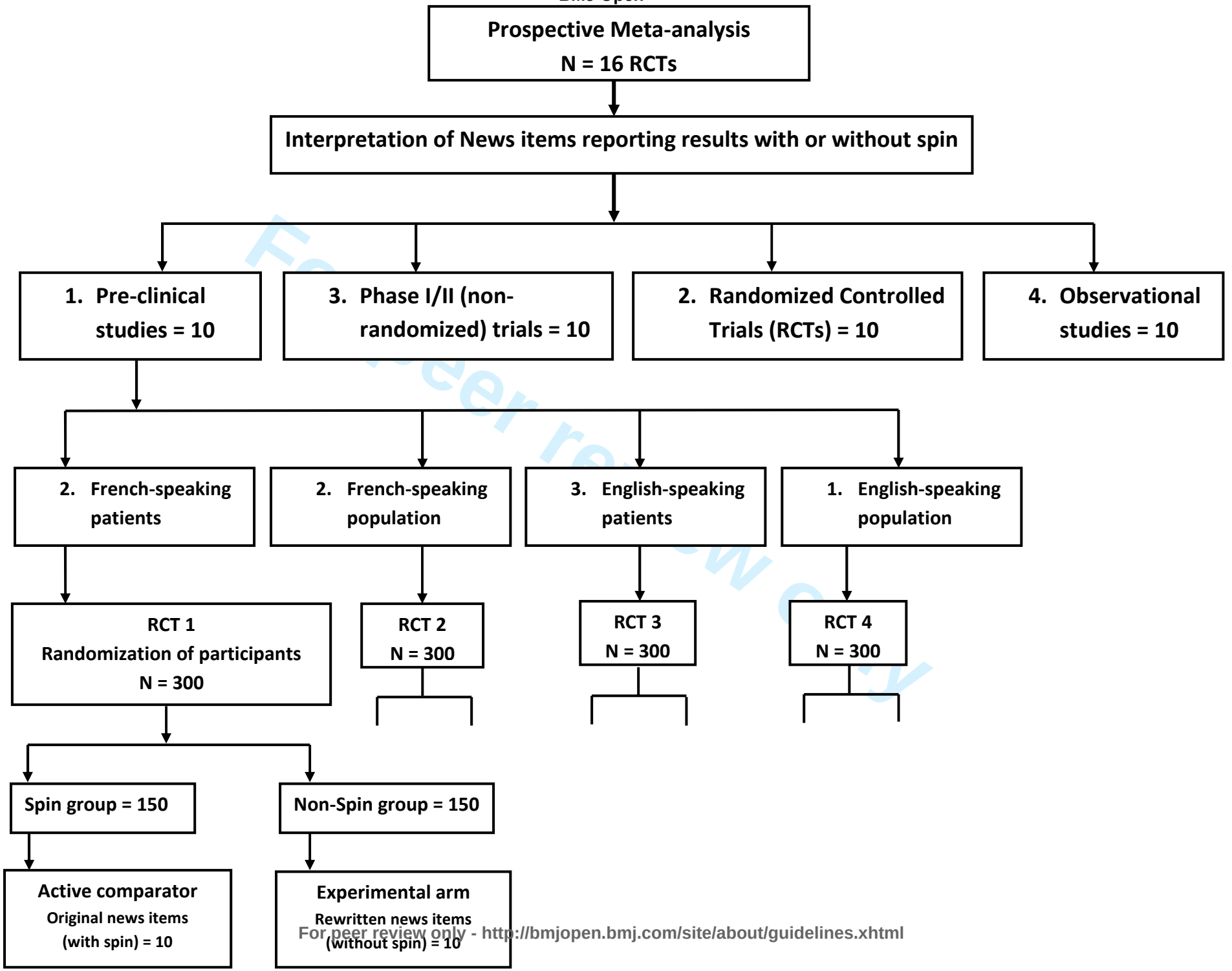
Each RCT will explore the interpretation of news items reporting 4 study designs: 1) pre-clinical studies, 2) phase I/II trials (non-randomized), 3) RCTs, and 4) observational studies. Each RCT will target 4 types of populations: 1) French-speaking patients, 2) French-speaking general public, 3) English-speaking patients, and 4) English-speaking general public.

**Table 1: Guidelines to remove spin**

| Spin | Interventions/modifications |
|---|---|
| **Spin in headline** | Delete the misleading information and report the appropriate information |
| **Spin in text** | |
| ***Misleading reporting*** | |
| • Misleading reporting of study design | Report the appropriate study design |
| • Not reporting study population if an animal study | Report animal study subjects |
| • Selective reporting of outcomes | Report the results for all primary outcomes. |
| • Not reporting adverse events | Report adverse events when higher in one group [We considered reporting more frequent and serious adverse events related to treatment primarily.] |
| • Use of linguistic spin | Delete linguistic spin |
| • Not reporting study limitations and caution specific to study design | Report the study limitations and cautions. The cautions with standardized text are described in table 2. |
| ***Misleading interpretation*** | |
| • Claiming a beneficial effect of intervention despite statistically non-significant results<br>• Claiming an equivalent beneficial effect of intervention despite statistically non-significant results in superiority RCTs | Delete this spin and use the generic wording, such as [Treatment A was not more effective on "primary outcome" than the comparator B in patients with....] |
| • Claiming the treatment is safe despite statistically non-significant results in treatment and comparison groups<br>• Claiming safety despite adverse events<br>• Claiming a causal effect despite non-randomized study design<br>• Claiming a beneficial effect despite small sample size not reported<br>• Claiming a beneficial effect despite lack of comparator<br>• Focus on p-value instead of magnitude of the effect (effect size) | Delete this spin; reword and provide the appropriate information when needed. |
| ***Misleading extrapolation*** | |
| • Animal study results to human application<br>• Preliminary study results to clinical application<br>• Study outcomes to other outcomes for the disease<br>• Study intervention to a different intervention<br>• Study participants to a larger or different population | Delete the inappropriate extrapolation |
| • Inappropriate implication for clinical or daily use | Delete the statement and clearly report the immediate unavailability in clinical practice |
| ***Author's/expert's statement (interview)*** | |
| | Delete the spin in the statement |
| | Report the caution or recommendation by study authors, reported in the relevant article when available. |

**Table 2: Reporting of cautions with standardized wording**

| Study design | Standardized text |
|---|---|
| • Animal or laboratory study | "The study was based on animals; it is impossible to know whether this treatment will work on humans or not." |
| • Small study | "These results are based on a small study; larger studies are needed to understand whether the treatment works across a large population." |
| • Uncontrolled study/Lack of comparator | "Everyone in this study took drug X. Without investigating patients who did not take that drug, it is impossible to know whether taking drug X accounted for the outcome". |
| • Controlled but not randomized study | "The study participants were not randomized. We do not know whether it was drug X or something else that really accounted for the effect observed." |
| • Important adverse event | "The benefit observed should be weighed against the adverse effects (or other downsides such as inconvenience, cost, etc)." |



## Appendix 1: An example of a news item with and without spin

| Original News (with spin) | Rewritten News (without spin) |
|---|---|
| **Now, 'sticky balls' that can prevent cancer spread**<br><br>Researchers have developed cancer-killing "sticky balls," that can destroy tumour cells in the blood and may prevent cancer spread.<br>The most dangerous and deadly stage of a tumour is when it spreads around the body.<br>Scientists at Cornell University, in the US, have designed nanoparticles that stay in the bloodstream and kill migrating cancer cells on contact, the BBC reported.<br>They said the impact was "dramatic" but there was "a lot more work to be done".<br>The team at Cornell attached a cancer-killing protein called Trail, which has already been used in cancer trials, and other sticky proteins to tiny spheres or nanoparticles.<br>When these sticky spheres were injected into the blood, they latched on to white blood cells.<br>Tests showed that in the rough and tumble of the bloodstream, the white blood cells would bump into any tumour cells which had broken off the main tumour and were trying to spread.The research showed the resulting contact with the Trail protein then triggered the death of the tumour cells.<br><br>Word count = 169 | **~~Now, 's~~Sticky balls' that ~~can~~ may prevent cancer spread in mice**<br><br>Researchers ~~have~~ are develop~~ed~~ing cancer-killing "sticky balls," that ~~can~~ may destroy tumour cells in the blood of mice ~~and may prevent cancer spread~~.<br>The most dangerous and deadly stage of a tumour is when it spreads around the body.<br>Scientists at Cornell University, in the US, have designed nanoparticles that stay in the bloodstream and may kill migrating cancer cells on contact, the BBC reported.<br>~~They said the impact was "dramatic" but there was "a lot more work to be done".~~<br>The biomedical engineers tested the new technology in live mice and human blood samples in cell culture.<br>The team at Cornell attached a ~~cancer-killing~~ protein called ~~Trail~~ TRAIL, which has already been used in cancer trials and other sticky proteins to tiny spheres or nanoparticles.<br>~~When these sticky spheres were injected into blood, they latched on to white blood cells.~~<br>Tests showed that in the rough and tumble of the bloodstream, the white blood cells would bump into any tumour cells which had broken off the main tumour and ~~were trying to spread~~ bind to the TRAIL protein. The research showed the resulting contact with the Trail protein then may ~~triggered~~ result in the death of the tumour cells.<br>However, it may take years to know whether this treatment will work for human or not. Indeed, less than 1% of the drugs tested on animals are approved for clinical use in patients.<br><br>Word count = 188 |

# Appendix 2: Informed consent

**Invitation letter**

**Objective:** Interpretation of health news items: an academic study

We invite you to participate in an international academic study to investigate people's understanding of health news items.

The study will require only a minimal amount of work on your part, and you will be helping to improve the reporting/communication of results related to medical research in health news for patients and the public.

Your participation would involve in reading a news item and answering five short questions about the findings in the news item. To avoid any biased interpretation, the description of the treatment and name of the study has been masked.

Your responses will be kept confidential. This study has been approved by INSERM, Institutional Review Board (IRB 00003888).

We will share with you the results of this study upon its completion.

You can complete the survey by XX

Or by copying and pasting the following link into your web browser: XX

With best wishes

Pr Isabelle Boutron (Paris Descartes University, INSERM UMR 1153, France)
Romana Haneef (Paris Descartes University, INSERM UMR 1153, France)
Dr. Amélie Yavchitz (French Cochrane Center, Paris, France)
Pr Philippe Ravaud (Paris Descartes University, INSERM UMR 1153, France)
Mr. Gabriel Baron (Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Paris, France)
Pr Ivan Oransky (New York University's Arthur Carter Journalism Institute, New York, USA)
Pr Gary Schwitzer (University of Minnesota, School of public health, Minnesota, USA)

If you prefer not to receive future reminders regarding this study, please click here.

**Next page**

**Please complete some simple information about yourself**

Your age:

Sex: Female Male

Do you have a chronic health condition yes/ no *(according to the answer, the participant will be directed to the survey dedicated to patients or to the public)*

Where are you currently located? France/ UK/ Other European country/ USA/ Canada/ South America/ Asia/ Oceania

Do you read health news items? yes/no

How many health news items do you read per month?

Do you rely on health news items to decide about your health?

What is your primary source to obtain information related to new treatments?

Physicians/family or friends/online health news/television/social media/other

**Submit**

**Next page**

**This news item describes a study evaluating a treatment published in a peer-reviewed journal.**

**Insertion of the news items**

**Based on the information reported in the news, please answer the following questions about the treatment:**

1. *What do you think is the probability that "treatment X" would be beneficial to patients? (scale, 0 [very unlikely] to 10 [very likely])* (Primary outcome)
2. *What do you think is the size of the potential benefit for patients? (scale, [none, small, moderate or large])*
3. *How safe do you think that this treatment X would be for patients? (scale, 0 [very unlikely] to 10 [very likely])*
4. *Do you think this treatment should be offered to patients in the short term? (scale, 0 [very unlikely] to 10 [very likely])*
5. *Do you think this treatment will make a difference in the existing clinical practice? (scale, 0 [absolutely no] to 10 [absolutely yes])*

Do you have any comments?

Write your comment here ...

**Submit**

Thank you very much for your participation in this study.

If you wish to receive the results of this study, please indicate your email address here.

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Page# in protocol |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | 1 |
| Identification | 1a | Identify the report as a protocol of a systematic review | 2 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 13 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 11 |
| Support: | | | 13 |
| Sources | 5a | Indicate sources of financial or other support for the review | |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | |
| **INTRODUCTION** | | | **4** |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| **METHODS** | | | **5** |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 5 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 5 |

| | | | |
|---|---|---|---|
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 5 |
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 6 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 6 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 6 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 6 & 7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 9 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | NA |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 9 & 10 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 10 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 10 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 12 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Page# in protocol |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym: | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | |
| Funding | 4 | Sources and types of financial, material, and other support | 13 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 & 13 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |
| **Introduction** | | | |

| | | | |
|---|---|---|---|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 1 |
| | 6b | Explanation for choice of comparators | 5 |
| Objectives | 7 | Specific objectives or hypotheses | 4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 8 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 9 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 9 |

| | | | |
|---|---|---|---|
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 10 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 8 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 9 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 5,6,7,8 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 8 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 10 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 10 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |

| | | | |
|---|---|---|---|
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 5 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 11 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 8 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 20 Appendix2 |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 21 Appendix2 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 13 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 13 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |

| | | | |
|---|---|---|---|
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 20 Appendix 2 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | 20 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# Interpretation of health news items reported with or without spin: Protocol for a prospective meta-analysis of 16 randomized controlled trials



| | |
|---|---|
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| Primary Subject Heading: | Research methods |
| Secondary Subject Heading: | Public health, Communication |
| Keywords: | Spin, Meta-analysis, Randomized controlled trials, Health News, Patients, General public |
| | |

# Interpretation of health news items reported with or without spin: Protocol for a prospective meta-analysis of 16 randomized controlled trials

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# ABSTRACT

**Introduction:** We aim to compare the interpretation of health news items reported with or without spin. "Spin" is defined as a misrepresentation of study results, regardless of motive (intentionally or unintentionally) that overemphasizes the beneficial effects of the intervention and overstates safety compared to that shown by the results.

**Methods and analysis:** We have planned a series of 16 RCTs to perform a prospective meta-analysis. We will select a sample of health news items reporting the results of 4 types of study designs, evaluating the effect of pharmacologic treatment and containing the highest amount of spin in the headline and text. News items reporting 4 types of studies will be included: 1) pre-clinical studies, 2) phase I/II (non-randomized) trials, 3) randomized controlled trials (RCTs), 4) observational studies. We will rewrite the selected news items and remove the spin. The original news and rewritten news will be appraised by 4 types of populations: 1) French-speaking patients, 2) French-speaking general public, 3) English-speaking patients, and 4) English-speaking general public. Each RCT will explore the interpretation of news items reporting one of the 4 study designs by each type of population and will include a sample size of 300 participants. The primary outcome will be participants' interpretation of the benefit of treatment after reading the news items: (*What do you think is the probability that treatment X would be beneficial to patients? (scale, 0 [very unlikely] to 10 [very likely])*.

This study will evaluate the impact of spin on the interpretation of health news reporting results of studies by patients and the general public.

**Ethics and dissemination:** This study has obtained ethics approval from the Institutional Review Board of INSERM, (registration No IRB00003888). The description of all the steps and the results of this prospective meta-analysis will be available online.

**Registration number:** CRD42017058941

## Strengths and limitations of this study

- This will be the first prospective meta-analysis of randomized controlled trials for interpretation of health news items reporting the results of studies with or without spin.
- It will address the impact of spin on the interpretation of health news by patients and the general public.
- The involvement of patients and the public may help to improve the reporting of medical research in health news.
- News stories are only one way that the public hears news about health.
- Logistically, the recruitment of large number of participants at the same time may be a challenge, but to manage this, participants will be recruited separately for each trial.

# INTRODUCTION

Health news is an important way to communicate updates about medical research to the public. News items reporting the results of medical research attract a large audience [1]. However, the quality of reporting in health news is uneven. The merits of a wide range of treatments and tests are overplayed, and harms are underplayed [2]. Several studies have shown the presence of spin (i.e., distorted presentation of study results) in health news [3-10]. Distorted facts can be misleading and can affect the behaviour of physicians, healthcare providers and patients [1 11 12]. However, little research has assessed whether spin can affect readers' interpretation [13]. Some studies have explored whether laypeople are able to recognize the tentativeness of research findings reported in media [14 15]. Kimmerle et al. found that negative framing and accentuation of the limited reliability of provisional research findings in a newspaper report made people more aware of the tentativeness of these findings [14]. In another work, the authors assessed the impact of some personality factors (i.e., scientific literacy, epistemology beliefs, and academic self-efficacy) and previous users' comments on an online website on laypeople's understanding of the tentativeness of medical research findings. Laypeople's understanding of the tentativeness of research findings was influenced by their personality factors and also by other users' comments contributed to the forum [15].

To our knowledge, no meta-analysis has assessed whether news items reported with spin can influence readers' interpretations.

Our hypothesis is that spin can influence the reader's interpretation of health news items. We aim to compare the interpretation of health news items reported with or without spin. We will focus on news items reporting studies evaluating the effect of a pharmacological treatment, containing the largest amount of spin in the headline and text, and receiving high levels of public attention online.

# METHODS

## Theoretical framework

Previous works have shown a high prevalence of spin in scientific articles [16-19] and in the mass media [8-10 20]. However, a question remains: Are readers influenced by spin or are they able to disentangle the appropriate interpretation from the news? In this study, we will consider only news items reporting studies evaluating pharmacological treatments where readers may overestimate the beneficial effect of the treatment if the news is reported with spin and change their behavior accordingly. We will consider different types of readers: patients and the main public. To increase generalisability we will also consider two different populations: located in the United States and in France.

## Definition of "spin"

In the context of this study, we define "spin" as a misrepresentation of study results, regardless of motive (intentionally or unintentionally) that overemphasizes the beneficial effects of the intervention and overstates safety compared to that shown by the results [16].

The definition of spin we used has been used for exploring spin in the scientific literature [8 13 16 19 21 22]. This definition does not take into account the notion of intent because it is impossible to distinguish between the two (i.e., intentional and unintentional spin) and the consequences for readers could be the same.

## Study design

We have planned a series of 16 randomized controlled trials (RCTs) to perform a prospective meta-analysis (MA), and a comparing the interpretation of health news items reported with or without spin. Each RCT will explore the interpretation of news items reporting one of 4 study designs: 1) pre-clinical studies, 2) phase I/II trials (non-randomized), 3) RCTs, and 4) observational studies. The news items reporting each study design will be assessed by 4 different

targeted populations: 1) French-speaking patients, 2) French-speaking general public, 3) English-speaking patients, and 4) English-speaking general public. Each RCT will be a parallel group with two-arms. In each RCT, participants will be randomly assigned to appraise health news items reported with or without spin *(see figure 1)*.

The planning, implementation, analysis and writing of this protocol will follow the SPIRIT [23] and PRISMA-P [24] guidelines. This study has obtained ethics approval from the Institutional Review Board of INSERM, (registration No IRB00003888), and the protocol is registered at PROSPERO website (CRD42017058941).

## News items with and without spin

### *Selection of news items with spin*

News items reporting studies evaluating a pharmacologic treatment that received a great deal of public attention online and contained a large amount of spin in the headline and text will be selected from a sample of news items retrieved from Altmetric Explorer.

### *Search strategy*

We will search for articles on "PubMed" using the following search strategy: field ((Randomized controlled trial[Publication Type] OR Observational study[Publication Type]) OR Meta-analysis[Publication Type]) OR Randomized[Title/Abstract]) OR controlled[Title/Abstract]) OR trial[Title/Abstract]) OR cross-sectional[Title/Abstract]) OR case-control[Title/Abstract]) OR cohort[Title/Abstract]) OR Meta-analysis[Title/Abstract]) OR systematic review[Title/Abstract]) AND (has abstract [text] AND ("2014/01/01"[PDAT] : "2014/06/30"[PDAT])). The publication period will be restricted to the first 6 months of 2014 to minimize the risk of recall bias among study participants.

To retrieve relevant news coverage of these articles, we will apply the "PubMed search details" on "Altmetric Explorer". The Web application Altmetric Explorer provides access to all sources

where the published study is mentioned online in the mass media and sorts the items according to the Altmetric score [25]. The Altmetric score is one way to quantify the public attention an article received in online news outlets, blogs and social media (https://www.altmetric.com/) (a high Altmetric score = high public attention).

***Screening process***

Screening will be performed in two steps: first, one researcher will systematically screen the retrieved Altmetric Explorer citations, which will be sorted from the highest to the lowest Altmetric score (i.e., highest to lowest amount of public attention), and will identify studies evaluating the effect of a pharmacological treatment, regardless of study design and study population (including human and animal/laboratory). For each study fulfilling eligibility criteria, the researcher will retrieve 1) the published article and 2) all related online news items available at Altmetric Explorer.

Second, the researcher will identify the news item with spin in the headline and text by using a standard scheme of spin [10 19]. When several news items have spin in the headline, the researcher will select the news item with the most spin in the text. We will include news items reported by general or medical news outlets or lay press whose target consumers are the general population.

As a quality procedure, a second researcher will confirm the eligibility of all included studies and screen 10% of the excluded studies.

The screening process will be performed sequentially, the studies being sorted from the highest to the lowest Altmetric score (i.e., highest to lowest public attention). We will include the first 40 studies fulfilling the eligibility criteria and relevant 40 news items containing the most spin in the headline and text: 10 reporting pre-clinical studies, 10 reporting phase I/II non-randomized trials, 10 news items reporting RCTs and 10 reporting observational studies.

*Identification and description of spin*

We will identify the spin in the headlines and text of selected news items and will classify them according to following 3 categories of spin — misleading reporting, misleading interpretation and misleading extrapolation — that were previously developed [10].

***Misleading reporting*** is defined as incomplete or inadequate reporting of any important information in the context of the research that could be misleading for the reader. This category includes 1) misleading reporting of study design; 2) not reporting study population (if an animal study); 3) selective reporting of outcomes favoring the beneficial effect of the treatment (e.g., statistically significant results for efficacy outcomes or statistically non-significant results for safety outcomes); 4) not reporting adverse events; 5) linguistic spin (i.e., any word or expression emphasizing the beneficial effect of the treatment [26]; 6) not reporting study limitations; 7) not reporting any caution about study design and results, and 8) any other type of misleading reporting not classified under the above section.

***Misleading interpretation*** is defined as an interpretation of the study results in news stories that is not consistent with the results reported in the scientific articles and overestimating the beneficial effect of the treatment. This category includes claiming 1) a beneficial effect of the treatment despite statistically non-significant results; 2) an equivalent effect of the treatment for statistically non-significant results in superiority RCTs; 3) that the treatment is safe for statistically non-significant results despite a lack of power; 4) safety of the treatment despite adverse events reported in the scientific articles; 5) a causal effect (i.e., implies a cause-and-effect relationship between the intervention being assessed and the outcome of interest [27]) despite a non-randomized study design; 6) a beneficial effect of the treatment despite a small sample size; and 7) a beneficial effect despite lack of a comparator as well as 8) focus on p-value instead of clinical importance; 9) interpretation of relative risk as absolute risk; and 10) any other type of misleading interpretation not otherwise classified.

***Misleading extrapolation*** is defined as overgeneralization of study results in news stories to different populations, interventions or outcomes that were not assessed in the study. This category includes extrapolating 1) animal study results to human application; 2) preliminary study results to clinical application; 3) the effect of study outcomes to other outcomes for the disease; 4) the beneficial effect of the study intervention to a different intervention (e.g., broccoli, which contains sulphoraphane, was claimed as beneficial by health news items, but the study evaluated the benefit of a sulphoraphane compound only); and 5) from the study participants to a larger or different population as well as 6) inappropriate implications for clinical or daily use (i.e., an improper recommendation or advice to use the intervention in clinical practice or daily use not supported by study results); and 7) any other types of extrapolation not otherwise classified.

All other spin that could not be classified with this scheme will be systematically recorded and secondarily classified.

## Construction of news without spin

### *Format of the news items*

Our aim is to keep the same context and format of the original news item and conceal the names of pharmacological treatments, authors and funders to avoid evaluation bias. Consequently, to rewrite the news items we will:

1. Keep the same context and structure
2. Create hypothetical names of reported pharmacological treatments
3. Conceal the names of study authors and experts by using different names selected based on the origin of the name from an online list of names including all countries of the world

(http://www.studentsoftheworld.info/penpals/stats.php3?Pays) to keep the news content natural.

4. Keep the name of the research institute/university/hospital where the study was conducted.
5. Replace the name of the funding source with standardized terms for profit or non-profit funding organizations.
6. Delete the name of the online news outlet, date the news story was published online, name of the journalist who wrote the news with spin, name of the medical journal in which the study was published, reference to the original article and trial registration number or name (if reported).

***Guidelines to remove spin in the news items***

To construct health news stories without spin, we will delete the spin identified in the headline and text and will add some caution, depending on context. The guidelines used to remove the spin are described in Table 1. The guidelines to add caution are in Table 2.

One researcher (RH) will identify and remove the spin in each news item selected (in the headline and text) and will rewrite the news story without spin, according to the guidelines described in Tables 1 and 2. Two researchers (IB) and (AY) will check the rewritten news items. Finally, a sample of the rewritten news stories will be checked by a researcher working in the field of medical journalism (IO). Appendix 1 provides an example of a news item reported with and without spin. Our sample of news will contain 80 news items [40 original news items (with spin) and 40 rewritten news items (without spin)].

### Translation of the news items reported with and without spin

All news items will be translated into French language to be used in RCTs involving French-speaking participants. One French native speaker researcher (AY) will validate the French translation of news items. Further, a French medical journalist will also validate the French translated news items.

### Population

We will compare the health news reported in English and French languages and will assess their interpretation by different types of populations to increase the generalisability of our results. Each RCT will target one of the four following study populations:

1. French-speaking patients
2. French-speaking general public
3. English-speaking patients
4. English-speaking general public

### Eligibility criteria

We will enroll participants older than 30 years.

### Recruitment strategy

To recruit participants, we will contact online communities of patients, patients' associations, popular health forums, and investigators of e-cohorts. We will also use the online platform (www.findparticipants.com) which enables access to thousands of interested participants to

participate in research studies worldwide. We will also advertise the study in hospitals and GP practices.

Each participant will provide an online informed consent at the time of enrollment.

We will send participants an invitation by email (appendix 2). If respondents agree to participate in the survey, an Internet link included in the invitation email will give them access to information regarding the study and a screening question asking them whether they are willing to participate in the study. If they answer yes, respondents will be randomly assigned to read 1 news item with spin or one news item without spin.

Invitation emails will be sent in waves until the planned number of participants log on and complete the assessment. A maximum of two reminders will be sent to participants.

## Interventions

We will compare the interpretation of "health news items" reported with spin (original news = active comparator) or without spin (rewritten news = experimental group).

## Random assignment

A random assignment sequence will be computer-generated by a statistician by using blocks of 10 (i.e., number of news items selected x 2) for each study design type. The list will not be disclosed to investigators. Allocation concealment will be assured by the use of a computerized random-assignment system. After randomization, participants will be asked to complete a questionnaire. Participants who log on and do not evaluate the news will be excluded and the news item will be automatically allocated to another participant.

## Blinding

Blinding of participants is not possible, but to minimize bias, participants will be blinded to the study hypothesis. All participants will be informed that they are participating in a survey about the interpretation of news reporting medical research that evaluates treatments. They will not be informed about the objectives and hypothesis of the study.

After the completion of study, each participant will be told about the study objectives, hypothesis and results.



**Study outcomes**

*Our primary outcome* will be participants' interpretation of the benefit of the treatment measured on a scale from 0 to10.

1. *What do you think is the probability that treatment X would be beneficial to patients? (scale, 0 [very unlikely] to 10 [very likely])*

*Secondary outcomes* are as follows:

2. *What do you think is the size of the potential benefit for patients? (scale, [none, small, moderate or large])*
3. *How safe do you think that treatment X would be for patients? (scale, 0 [very unsafe] to 10 [very safe])*
4. *Do you think this treatment should be offered to patients in the short term? (scale, 0 [ absolutely no] to 10 [ absolutely yes])*
5. *Do you think this treatment will make a difference in the existing clinical practice? (scale, 0 [absolutely no] to 10 [absolutely yes])*

These study outcomes are surrogate markers measuring the perception by readers of the treatments' efficacy, safety, availability and use in current clinical practice.

## Sample size

Each participant will read a news item with or without spin. We want to assess a mean difference of 1.0 for the primary outcome between groups on a 0-10 scale, with a standard deviation of 2.5 [13]. For each RCT, a sample of 266 assessments of news items will be needed to detect an effect size of 0.4 with a power of 90% and α risk of 5% for each RCT. Each news item will be read the same number of times (balanced design) and we will to take into account clustering due to the fact that a news items will be read many times. To achieve this, we will use a sample size of 300 participants (150 in each group) in each RCT (i.e., an inflation factor of about 1.1). Therefore, each news item will be assessed 15 times in each group (10 news items with or without spin for 150 participants) for each RCT.

## Statistical analysis

The statistical analysis will be undertaken by a statistician who will use R v2.15.1 (R foundation for Statistical Computing, Vienna, Austria) at the Center for Clinical Epidemiology, Paris, France. All outcomes will be quantitative and the number of participants and news items will be balanced in each group. For each RCT, the following analysis will be done: The differences between groups will be analyzed by using a linear mixed model with a fixed group effect and random group effect and news items–group interaction effects. Random effects will allow us to account for the following 2 levels of clustering: within-group clustering as a result of the news (each news item will be assessed 15 times in each group) and between-group clustering (pairing between the news used in the 2 arms of the trial). Inferences will be based on the restricted maximum likelihood. This model will compare the mean difference between 2 arms for each trial. For primary and secondary outcomes, we will estimate the difference between means with 95% confidence intervals (CIs). $P$ <0.05 will be considered statistically significant.

Finally, after analyzing each RCT separately, a prospective meta-analysis will be done to summarize intervention effects. The mean difference with 95% CIs will be estimated by using a random-effects model based on the DerSimonian-Laird method. Forest plots will be created for visual interpretation of results. The heterogeneity will be assessed by $X^2$ test *(P <0.05)* and degree of heterogeneity by the $I^2$ statistic *(>75%)* to assess statistical significance (Higgins JPT et al, 2014). We will also assess the variance ($\tau^2$) between trials.

## STUDY DURATION

The total duration of this study will be 24 months. Expected period of inclusion of participants will also be 24 months and the duration of participation per participant/patient will be 1 hour. The anticipated start date of trials will be June, 2017.

# DISCUSSION

To best of our knowledge, we present the first prospective meta-analysis of randomized controlled trials for interpretation of health news items reporting the results of studies with or without spin.

We have designed 16 randomized controlled trials which will focus on interpretation of news items reporting results of 4 types of study designs: 1) pre-clinical studies, 2) phase I/II trials (non-randomized), 3) RCTs, and 4) observational studies. There will be 80 news items reporting these study designs (20 new items / study design: 10 original news items with spin + 10 rewritten news items without spin). Each RCT will target one of the 4 types of populations: 1) French-speaking patients, 2) French-speaking general public, 3) English-speaking patients, and 4) English-speaking general public. In total, 4800 participants will be involved in 16 planned RCTs (300 participants/ RCT). Once the planned RCTs are completed, then the results of different RCTs will be included to perform a meta-analysis.

The concept of prospective meta-analysis allows us to compare the interpretation of health news stories reporting results of studies with or without spin by different types of populations. This new form of synthesis of evidence answers the question of whether spin can influence patients' and the publics' interpretation of health news.

We will document all practical issues and difficulties encountered to demonstrate that this type of synthesis of evidence is feasible. We are aware of some challenges, such as recruitment of participants. Logistically, the recruitment of large number of participants at the same time may be a challenge, but to manage this, participants will be recruited separately for each trial.

# EXPECTED RESULTS

This study will evaluate the impact of spin on patients' and the public's interpretation of news items reporting results of studies.

## Supplementary Data

Appendix1: An example of a news item with and without spin

Appendix 2: Informed consent

# MODIFICATIONS MADE IN THE PROTOCOL SUBMITTED TO ETHICAL COMMITTEE

We made following changes in the protocol submitted to the ethical committee:

## Rewriting news items

- Word count: The condition to keep the word count of ±20% from original news to rewritten news items is deleted.
- Concealment: The name of the research institute/university/hospital where the study was conducted will be kept in the rewritten news items.
- Guidelines to remove spin: We will also report the caution or recommendation by study authors, reported in the related article when available.

## Survey questionnaire

- We merged two questions related to demographic information into one: How often do you read news items? Never/sometimes (once per month)/often(once per week)/daily

## Guidelines

- We report SPIRIT and PRISMA-P guidelines to follow for protocols of clinical trials and meta-analysis respectively.

**Acknowledgements**

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**Contributors**

RH: Helped with conception of study design, selecting news items, rewriting news items and wrote the draft of the protocol, AY: Helping with validation of rewritten the news items and French translation of selected news items, PR: Conception of study design, GB: Helped to write the statistical analysis, IO: Helped with survey questionnaire and validation of rewritten news items, GS: Helped with survey questionnaire, IB: Conception of study design, validating rewritten news items, and helped to write the draft of the protocol.

All authors read and approved the final protocol.

**Funding**

None

**Competing interests**

None declared

## Data sharing statement

This article is the protocol of a prospective meta-analysis. The authors plan to report transparently all the planned trials and will provide open access to all extracted data for each trial.

## Open Access



## Ethics and dissemination

"This study obtained ethics approval from the Institutional Review board of INSERM (Registration No: IRB0003888), and the protocol is registered at the PROSPERO website (CRD42017058941). We report SPIRIT [23]and PRISMA-P [24] guidelines for protocols of clinical trials and meta-analyses, respectively. The results of this meta-analysis will be disseminated as a published article. Upon the completion of this study, the results will be sent to all participants."

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**Figure 1: Series of 16 RCTs that will be included in the prospective meta-analysis**

Each RCT will explore the interpretation of news items reporting 4 study designs: 1) pre-clinical studies, 2) phase I/II trials (non-randomized), 3) RCTs, and 4) observational studies. Each RCT will target 4 types of populations: 1) French-speaking patients, 2) French-speaking general public, 3) English-speaking patients, and 4) English-speaking general public.

**Table 1: Guidelines to remove spin**

| Spin | Interventions/modifications |
|---|---|
| **Spin in headline** | Delete the misleading information and report the appropriate information |
| **Spin in text** | |
| ***Misleading reporting*** | |
| • Misleading reporting of study design | Report the appropriate study design |
| • Not reporting study population if an animal study | Report animal study subjects |
| • Selective reporting of outcomes | Report the results for all primary outcomes. |
| • Not reporting adverse events | Report adverse events when higher in one group [We considered reporting more frequent and serious adverse events related to treatment primarily.] |
| • Use of linguistic spin | Delete linguistic spin |
| • Not reporting study limitations and caution specific to study design | Report the study limitations and cautions. The cautions with standardized text are described in table 2. |
| ***Misleading interpretation*** | |
| • Claiming a beneficial effect of intervention despite statistically non-significant results<br>• Claiming an equivalent beneficial effect of intervention despite statistically non-significant results in superiority RCTs | Delete this spin and use the generic wording, such as [Treatment A was not more effective on "primary outcome" than the comparator B in patients with....] |
| • Claiming the treatment is safe despite statistically non-significant results in treatment and comparison groups<br>• Claiming safety despite adverse events<br>• Claiming a causal effect despite non-randomized study design<br>• Claiming a beneficial effect despite small sample size not reported<br>• Claiming a beneficial effect despite lack of comparator<br>• Focus on p-value instead of magnitude of the effect (effect size) | Delete this spin; reword and provide the appropriate information when needed. |
| ***Misleading extrapolation*** | |
| • Animal study results to human application<br>• Preliminary study results to clinical application<br>• Study outcomes to other outcomes for the disease<br>• Study intervention to a different intervention<br>• Study participants to a larger or different population | Delete the inappropriate extrapolation |
| • Inappropriate implication for clinical or daily use | Delete the statement and clearly report the immediate unavailability in clinical practice |
| ***Author's/expert's statement (interview)*** | |
| | Delete the spin in the statement |
| | Report the caution or recommendation by study authors, reported in the relevant article when available. |

**Table 2: Reporting of cautions with standardized wording**

| Study design | Standardized text |
|---|---|
| • Animal or laboratory study | "The study was based on animals; it is impossible to know whether this treatment will work on humans or not." |
| • Small study | "These results are based on a small study; larger studies are needed to understand whether the treatment works across a large population." |
| • Uncontrolled study/Lack of comparator | "Everyone in this study took drug X. Without investigating patients who did not take that drug, it is impossible to know whether taking drug X accounted for the outcome". |
| • Controlled but not randomized study | "The study participants were not randomized. We do not know whether it was drug X or something else that really accounted for the effect observed." |
| • Important adverse event | "The benefit observed should be weighed against the adverse effects (or other downsides such as inconvenience, cost, etc)." |

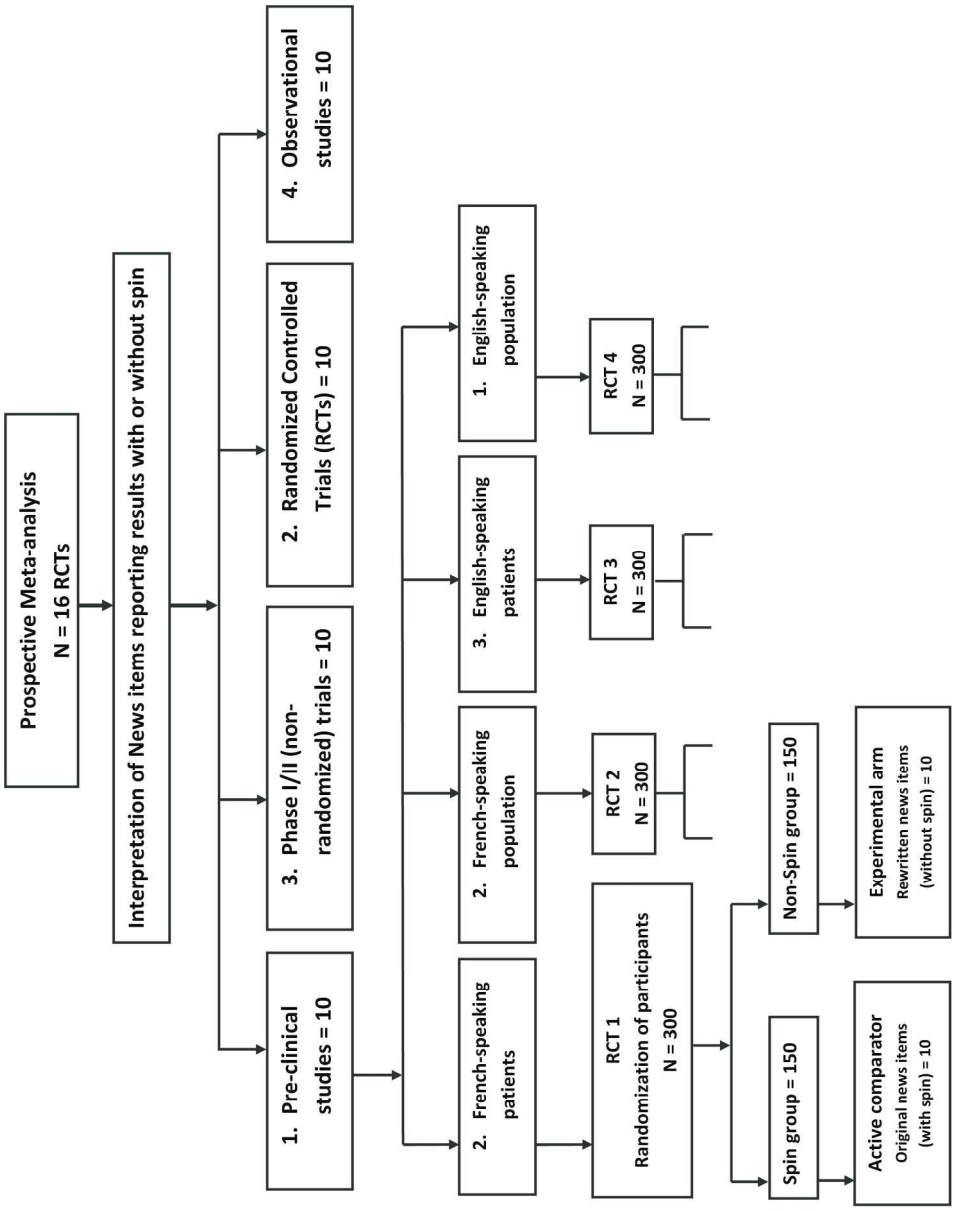


Figure 1: Series of 16 RCTs that will be included in the prospective meta-analysis

197x249mm (300 x 300 DPI)

## Appendix 1: An example of a news item with and without spin

| Original News (with spin) | Rewritten News (without spin) |
|---|---|
| **Now, 'sticky balls' that can prevent cancer spread**<br><br>Researchers have developed cancer-killing "sticky balls," that can destroy tumour cells in the blood and may prevent cancer spread.<br>The most dangerous and deadly stage of a tumour is when it spreads around the body.<br>Scientists at Cornell University, in the US, have designed nanoparticles that stay in the bloodstream and kill migrating cancer cells on contact, the BBC reported.<br>They said the impact was "dramatic" but there was "a lot more work to be done".<br>The team at Cornell attached a cancer-killing protein called Trail, which has already been used in cancer trials, and other sticky proteins to tiny spheres or nanoparticles.<br>When these sticky spheres were injected into the blood, they latched on to white blood cells.<br>Tests showed that in the rough and tumble of the bloodstream, the white blood cells would bump into any tumour cells which had broken off the main tumour and were trying to spread.The research showed the resulting contact with the Trail protein then triggered the death of the tumour cells.<br><br>Word count = 169 | **~~Now, 's~~Sticky balls' that ~~can~~ may prevent cancer spread in mice**<br><br>Researchers ~~have~~ are develop~~ed~~ing cancer-killing "sticky balls," that ~~can~~ may destroy tumour cells in the blood of mice ~~and may prevent cancer spread~~.<br>The most dangerous and deadly stage of a tumour is when it spreads around the body.<br>Scientists at Cornell University, in the US, have designed nanoparticles that stay in the bloodstream and may kill migrating cancer cells on contact, the BBC reported.<br>~~They said the impact was "dramatic" but there was "a lot more work to be done".~~<br>The biomedical engineers tested the new technology in live mice and human blood samples in cell culture.<br>The team at Cornell attached a ~~cancer-killing~~ protein called ~~Trail~~ TRAIL, which has already been used in cancer trials and other sticky proteins to tiny spheres or nanoparticles.<br>~~When these sticky spheres were injected into blood, they latched on to white blood cells.~~<br>Tests showed that in the rough and tumble of the bloodstream, the white blood cells would bump into any tumour cells which had broken off the main tumour and ~~were trying to spread~~ bind to the TRAIL protein. The research showed the resulting contact with the Trail protein then may ~~triggered~~ result in the death of the tumour cells.<br>However, it may take years to know whether this treatment will work for human or not. Indeed, less than 1% of the drugs tested on animals are approved for clinical use in patients.<br><br>Word count = 188 |

# Appendix 2: Informed consent

## Invitation letter

**Objective:** Interpretation of health news items: an academic study

We invite you to participate in an international academic study to investigate people's understanding of health news items.

The study will require only a minimal amount of work on your part, and you will be helping to improve the reporting/communication of results related to medical research in health news for patients and the public.

Your participation would involve in reading a news item and answering five short questions about the findings in the news item. To avoid any biased interpretation, the description of the treatment and name of the study has been masked.

Your responses will be kept confidential. This study has been approved by INSERM, Institutional Review Board (IRB 00003888).

We will share with you the results of this study upon its completion.

You can complete the survey by XX

Or by copying and pasting the following link into your web browser: XX

With best wishes

Pr Isabelle Boutron (Paris Descartes University, INSERM UMR 1153, France)
Romana Haneef (Paris Descartes University, INSERM UMR 1153, France)
Dr. Amélie Yavchitz (French Cochrane Center, Paris, France)
Pr Philippe Ravaud (Paris Descartes University, INSERM UMR 1153, France)
Mr. Gabriel Baron (Centre d'Épidémiologie Clinique, Hôpital Hôtel-Dieu, Paris, France)
Pr Ivan Oransky (New York University's Arthur Carter Journalism Institute, New York, USA)
Pr Gary Schwitzer (University of Minnesota, School of public health, Minnesota, USA)

If you prefer not to receive future reminders regarding this study, please click here.

**Next page**

**Please complete some simple information about yourself**

Your age:

Sex: Female Male

Do you have a chronic health condition yes/ no *(according to the answer, the participant will be directed to the survey dedicated to patients or to the public)*

Where are you currently located? France/ UK/ Other European country/ USA/ Canada/ South America/ Asia/ Oceania

How often do you read news items? Never/sometimes (once per month)/often (once per week)/daily

Do you rely on health news items to decide about your health?

What is your primary source to obtain information related to new treatments?

Physicians/family or friends/online health news/television/social media/other

**Submit**

**Next page**

**This news item describes a study evaluating a treatment published in a peer-reviewed journal.**

**Insertion of the news items**

**Based on the information reported in the news, please answer the following questions about the treatment:**

1. *What do you think is the probability that "treatment X" would be beneficial to patients? (scale, 0 [very unlikely] to 10 [very likely])* (Primary outcome)
2. *What do you think is the size of the potential benefit for patients? (scale, [none, small, moderate or large])*
3. *How safe do you think that this treatment X would be for patients? (scale, 0 [very unsafe] to 10 [very safe])*
4. *Do you think this treatment should be offered to patients in the short term? (scale, 0 [absolutely no] to 10 [absolutely yes])*
5. *Do you think this treatment will make a difference in the existing clinical practice? (scale, 0 [absolutely no] to 10 [absolutely yes])*

Do you have any comments?

Write your comment here ...

**Submit**

Thank you very much for your participation in this study.

If you wish to receive the results of this study, please indicate your email address here.

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Page# in protocol |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | 1 |
| Identification | 1a | Identify the report as a protocol of a systematic review | 1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2, 6, 20 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 19 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 18 |
| Support: | | | 19 |
| Sources | 5a | Indicate sources of financial or other support for the review | |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | |
| **INTRODUCTION** | | | **4** |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| **METHODS** | | | **5** |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 6, 7 |

| | | | |
|---|---|---|---|
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 6 |
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 7, 8 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 6, 7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 7, 8 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 7, 8, 9, 10 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 13 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | NA |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 12,13 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 13, 14 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 14 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | NA |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 16 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Page# in protocol |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym: | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | |
| Funding | 4 | Sources and types of financial, material, and other support | 19 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1 & 19 |
| | 5b | Name and contact information for the trial sponsor | 1 |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |
| **Introduction** | | | 4 |

| | | | |
|---|---|---|---|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4 |
| | 6b | Explanation for choice of comparators | 6,10 |
| Objectives | 7 | Specific objectives or hypotheses | 4 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 11 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 12 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 13 |

| | | | |
|---|---|---|---|
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 15 |
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 14 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 11 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 12 |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 12 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 12 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 12 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | **6-10** |

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 6-10 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 11 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 14 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 10 |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |

| | | | |
|---|---|---|---|
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | **20** |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 2,6,20 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 18 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 17(appendix:2) |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | 17 Appendix:2 |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 17 Appendix:2 |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 19 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 19 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |

| | | | |
|---|---|---|---|
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 20 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | 17 |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | 17 Appendix:2 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | |

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