



# Exploring how and when to categorise intermediate outcomes as surrogate endpoints

Please see the participant information sheet [https://www.gla.ac.uk/media/Media\\_933455\\_smx.pdf](https://www.gla.ac.uk/media/Media_933455_smx.pdf) and privacy notice [https://www.gla.ac.uk/media/Media\\_933454\\_smx.pdf](https://www.gla.ac.uk/media/Media_933454_smx.pdf).

We will present you with **intermediate outcomes** used in recent trials along with links to published protocols or reports. We will also provide **you with reasons for and against considering the outcomes as surrogate endpoints**. You then have a chance to answer **Yes, No, or uncertain** to each of the intermediate outcome. The reasons we provide may not be exhaustive and it is optional to provide free-text comments explaining your choice.

At the end of page, use **Next** to move to next section of the survey

\* Required

## Consent

1. I have read and understood the participant information sheet and privacy notice and agree to take part in this study \*

☐ Yes

☐ No

## Participant characteristics

2. What is your primary professional role? \*

- ☐ Healthcare professional/Clinician
- ☐ Trial investigator
- ☐ Trial methodologist
- ☐ Epidemiologist
- ☐ Surrogate content expert
- ☐ Statistician
- ☐ Patient and Public Involvement representative/contributor/partner
- ☐ Research funding board/panel member
- ☐ Journal editor/editorial member
- ☐ Regulatory assessor
- ☐ HTA expert
- ☐ Trial manager
- ☐ Clinical guideline developer
- ☐ Other

...

3. How many years of the experience/expertise in trials and/or use of surrogate endpoints do you have?

## Categorising intermediate outcomes as surrogate endpoints

### 4. Surgical site infection

Trial title: Comparison of intravenous versus combined oral and intravenous antimicrobial prophylaxis (COMBINE) for the prevention of surgical site infection in elective colorectal surgery: study protocol for a multicentre, double-blind, randomised controlled clinical trial

Verbatim description of outcome: *The primary outcome measure is the proportion of patients with any SSI within 30 days after surgery. SSI are classified as being superficial, deep and/or organ-space infection on the basis of validated and well-defined criteria developed by the Centers for Disease Control and Prevention*[ref]

Link to trial: <https://bmjopen.bmj.com/content/8/4/e020254.long>

Why would it be surrogate?

- SSI is associated with other distal outcomes as the authors note: "*SSIs are associated with a longer hospital stay, a fivefold likelihood of postoperative readmission after hospital discharge and a twofold to threefold increase in costs of care, [refs] and are an independent predictor of mortality in surgical patients [ref]*"
- The SSI measurement in the trial is not a direct measure of what a patient feels (it's not a patient reported measure): "*SSI are classified as being superficial, deep and/or organ-space infection on the basis of validated and well-defined criteria developed by the Centres for Disease Control and Prevention [ref]*"

Why would it not be surrogate?

- The intervention intent is to prevent SSI, so it is the trial's target outcome.
- SSI can be perceived by the patient unlike biomarkers.

\*

**Surgical site infection (SSI): Do you consider it a surrogate endpoint?**

- ☐ Yes
- ☐ No
- ☐ Uncertain

5. Optional free-text comment on your answer above

## 6. Smoking cessation

Trial title: Randomised, placebo-controlled, double-blind, double-dummy, multicentre trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine: the ECSMOKE trial protocol

Verbatim description of outcome: *Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9–12) of the treatment period of 3 months. Definition: self-report of no smoking during the previous 2 weeks and expired air CO  $\leq$ 8 ppm. At visit 4 at week 10 after TQD, that is, 11 weeks after treatment initiation AND at visit 5, week 12 after TQD, that is, 13 weeks after treatment initiation.*

Link to trial: <https://bmjopen.bmj.com/content/9/5/e028832.long>

Why would it be a surrogate?

- Smoking cessation is associated with lower mortality and particularly from a specific age as the authors point out: "*Smoking cessation before the age of 40 reduces the risk of death compared with continued smoking by 90% [ref]*"
- The measurement of smoking cessation included a sign which is not a patient reported outcome: "*self-report of no smoking during the previous 2 weeks and expired air CO  $\leq$ 8 ppm.*"

Why would it not be a surrogate?

- The therapeutic intent of the intervention is to stop smoking and not to increase survival so smoking cessation is a target outcome.
- Smoking cessation has benefits to an individual which can be perceived.
- The measurement of smoking cessation included a patient reported outcome: "*self-report of no smoking during the previous 2 weeks and expired air CO  $\leq$ 8 ppm.*"

\*

**Smoking cessation: Do you consider it a surrogate endpoint?**

- ☐ Yes
- ☐ No
- ☐ Uncertain

7. Optional free-text comments on your answer above

## 8. Childhood obesity

Trial title: Effectiveness of a childhood obesity prevention programme delivered through schools, targeting 6 and 7 year olds: cluster randomised controlled trial (WAVES study)

Verbatim description of outcome: *The primary outcome for clinical effectiveness specified in our analysis plan and trial protocol was the difference in BMI z scores between arms at 15 and 30 months.*

Link to trial: <https://www.bmj.com/content/360/bmj.k211>

Why would it be a surrogate?

- Childhood obesity has health consequences at present but also predicts adult obesity as authors note: *"In addition to physical and psychosocial health consequences in these early years, childhood excess weight is an important predictor of obesity in adulthood, [ref] with additional adverse health and economic [ref] effects."*
- We can further say adult obesity predicts severe morbidity and mortality hence childhood obesity is a surrogate of another surrogate.
- The measurement of obesity in this trial using *"between arm difference in body mass index (BMI) z score at 15 and 30 months"* is not a direct measure of what an individual feels (it is not a patient reported outcome) and has to be inferred using BMI

Why would it not be a surrogate?

- The therapeutic intent of the intervention is to prevent obesity, so BMI is the target outcome.
- Obesity can be perceived by the individual unlike biomarkers.

\*

**Childhood obesity: Do you consider it a surrogate endpoint?**

- ☐ Yes
- ☐ No
- ☐ Uncertain

9. Optional free-text comment on your answer above

## 10. Severity of symptoms

Trial title: The STOP-AB trial protocol: efficacy and safety of discontinuing patient antibiotic treatment when physicians no longer consider it necessary

Verbatim description of outcome: *The primary outcome measure was the duration of severe symptoms. Each symptom was scored using a six-point Likert scale and symptoms scoring 5 or 6 was considered as severe. We included common symptoms such as feeling of fever, discomfort or general malaise, cough, difficulty in sleeping and changes in everyday life in all patients, and specific symptoms according to the condition (table 1).*[ref]

Link to trial: <https://bmjopen.bmj.com/content/7/5/e015814>

Why would it be a surrogate?

- Symptoms however severe can be regarded as surrogate endpoints as they predict other distal outcomes such health-related quality of life or hospitalisation

Why would it not be a surrogate?

- The intervention is aimed at a self-limiting condition (hospitalisation and mortality from condition is very rare) and therefore the therapeutic intent on symptoms can be considered the target outcome.
- Symptoms can be regarded as direct measures of what a patient feels hence a target outcome.

\*

**Severity of symptoms: Do you consider it a surrogate endpoint?**

- ☐ Yes
- ☐ No
- ☐ Uncertain

11. Optional free-text comment on your answer above

## 12. Rankin scale

This is a clinical scale measuring symptoms, different forms of disability, and death.

Trial title: Thrombectomy for Stroke in the Public Health Care System of Brazil

Verbatim description of outcome: *The primary outcome was disability at 90 days, evaluated by the distribution of scores on the modified Rankin scale. Assessment was based on central adjudication by consensus of two certified neurologists, who were unaware of the treatment assignments and who viewed video recordings of structured patient or family interviews.[ref]*

Link to trial: <https://www.nejm.org/doi/10.1056/NEJMoa2000120>

Why would it be a surrogate?

- Symptoms and moderate forms of disability can be argued to be predictors of health-related quality of life and mortality hence surrogate endpoints
- Categorisation on the clinical scale was done by clinicians not directly by patients

Why would it not be a surrogate?

- The authors note that the therapeutic intent of the trial was improving functional outcomes hence a target outcome.
- Symptoms and disability are measures of what a patient feels or functions hence target outcomes

\*

**Symptoms and disability: Do you consider either of both as surrogate endpoints?**

- ☐ Yes, for symptoms.
- ☐ Yes, for symptoms and mild and moderate disability.
- ☐ Yes, for symptoms and all forms of disability.
- ☐ No to either
- ☐ Uncertain

13. Optional free-text comment on your answer above

#### 14. Spontaneous vaginal birth

Trial title: Upright versus lying down position in second stage of labour in nulliparous women with low dose epidural: BUMPES randomised controlled trial

Verbatim description of outcome: *The primary outcome measure was spontaneous vaginal birth.*

Link to trial: <https://www.bmj.com/content/359/bmj4471>

Why would it be a surrogate?

- Spontaneous vaginal birth can be viewed as a predictor of distal outcomes such as health-related quality of life for the mother and better health outcomes for the new-born
- Spontaneous vaginal birth is a sign and not a direct measure of what a patient feels or functions

Why would it not be a surrogate?

- The intervention intent was to increase likelihood of spontaneous vaginal birth so this could be considered the target outcome.

\*

**Spontaneous vaginal birth: Do you consider it a surrogate endpoint?**

- ☐ Yes
- ☐ No
- ☐ Uncertain

15. Optional free-text comment on your answer above



## General comments and sign off

16. Any other general comments regarding this exercise?

17. Would you want to be acknowledged in publications as a participant in this study? \*

☐ Yes

☐ No

18. Please type your name that you would want used in the acknowledgment list

---

This content is neither created nor endorsed by Microsoft. The data you submit will be sent to the form owner.

 Microsoft Forms