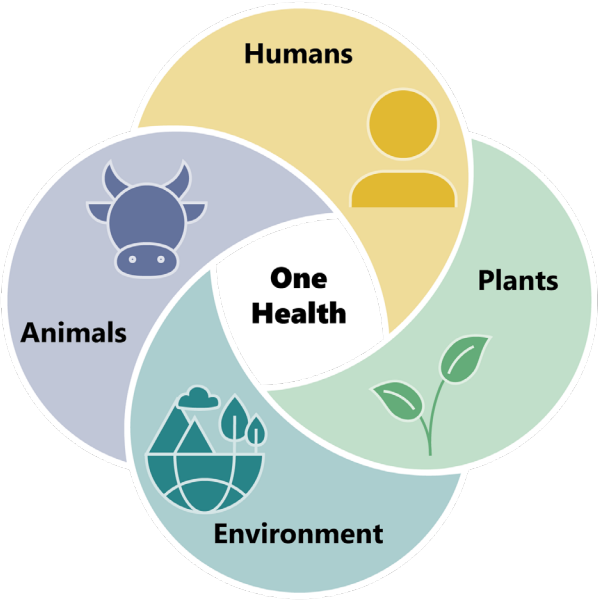
A brief outline of principles for validation of a surrogate endpoint - options for qualification advice



Elisabeth Wischnitzki

EMRN workshop on Geographic Atrophy endpoints – 29 April 2026

Surrogate endpoints - principles

Principles

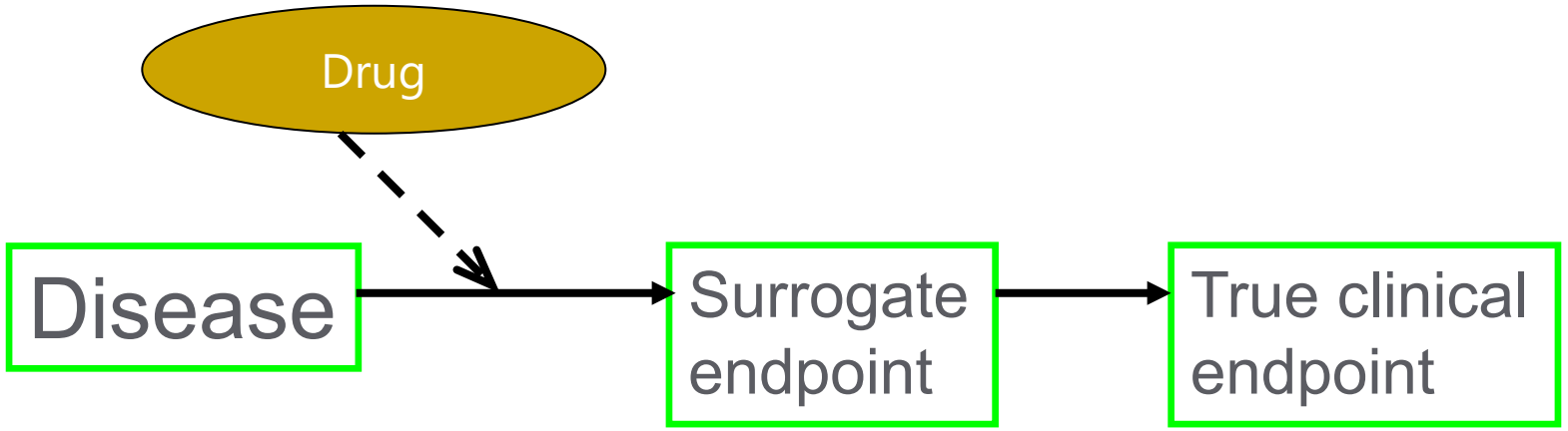
To substitute for a primary clinical efficacy endpoint in a pivotal trial:

- Show that with an investigative medical product, a **change in surrogate endpoint** (e.g. anatomical) **predicts /corresponds to change in clinical efficacy endpoint** (i.e. symptoms/function) (E9)
- Minimal clinically important difference (MCID) should be established

Concerns: surrogate may not be a true predictor, or quantify the benefit (correlation is not sufficient)

Surrogate endpoints

Ideal treatment, surrogate and clinical outcome relationships

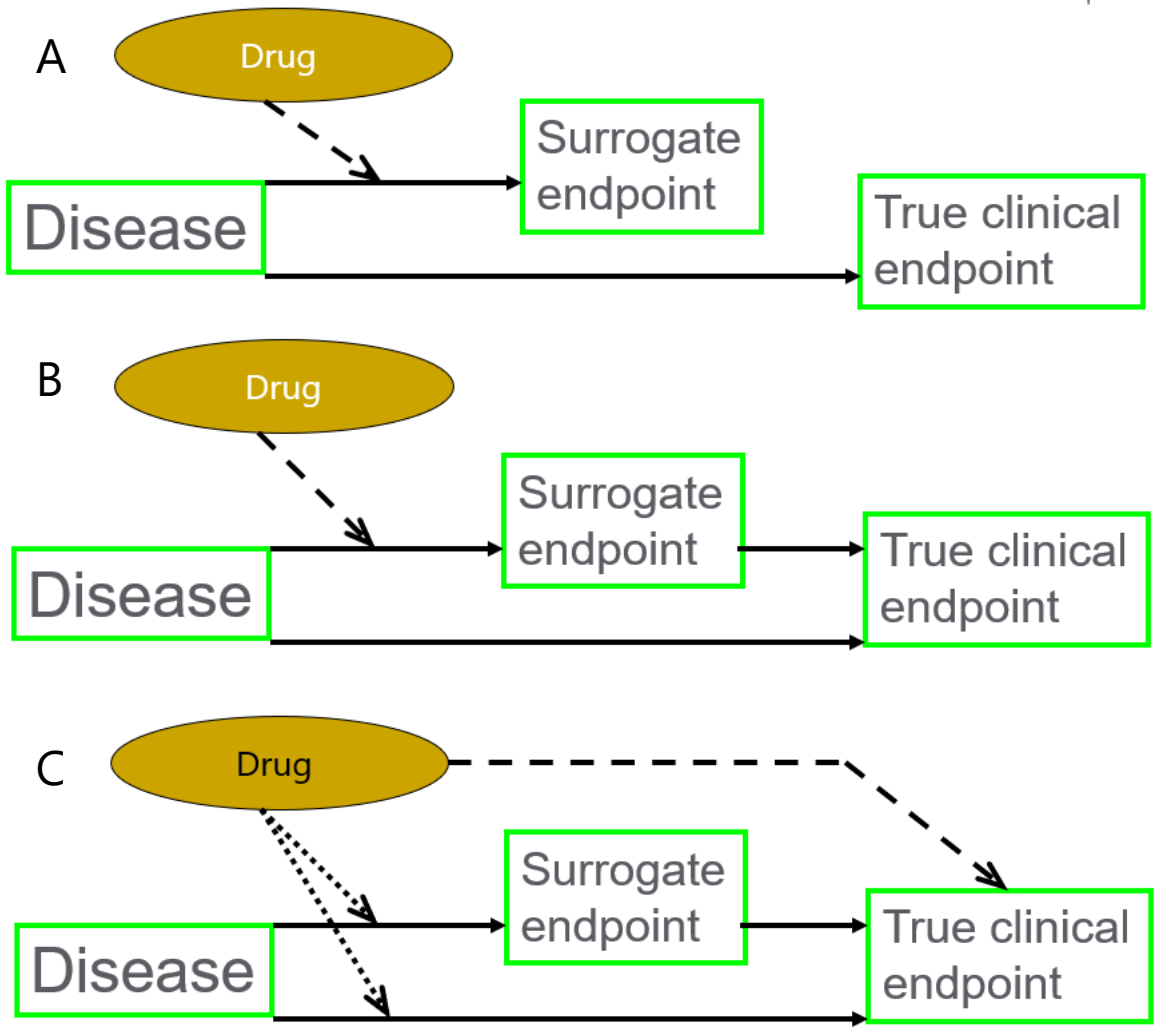


Surrogate endpoints

Potential concerns

- Surrogate is not in causal pathway (A)
- Drug affects only one of several causal pathways (B)
- The surrogate is **only one measure** of drug effect, usually the short-term effect presumed to be of value. Drugs may have other effects. (C)

Using surrogate endpoint misleading **false positive** or **false negative** conclusion can be made.



Fleming & DeMets, 1996

Surrogate endpoints - principles

Validation options

- Investigational trial data; collect exploratory, confirmatory data
- Understand the biological relationship of the surrogate and the clinical outcome
- Understand the mechanisms of action of the intervention in the condition
- Epidemiological evidence that the parameter is a risk factor

- **Understand predictive value of the surrogate for the clinical outcome**
  - **Surrogate must be on the causal pathway**
  - **change in surrogate endpoint predicts /corresponds to change in clinical efficacy endpoint**

- Correlation alone is not sufficient

- Study measurement properties

Geographic Atrophy (GA) primary endpoint

What are the concerns about the current anatomical endpoints, e.g. slowing GA lesion progression?

Concerns:

- Anatomical / imaging endpoints are **surrogate endpoints**
- Do not yield a measure of clinical benefit that can be weighed directly against adverse effects

- CHMP needs to understand when and to what extent a certain lesion size reduction would turn into perceivable patient benefit with treatment.

Geographic Atrophy (GA) primary endpoint

Anatomical endpoint as primary endpoint

To use an Anatomical endpoint as primary endpoint

- It needs to be shown to be a **valid surrogate** of visual function,
  - Need to **show** that a treatment which **slows the growth of geographic atrophy** lesions, will lead to a clinically **meaningful benefit** for patients.

This justification could be based

- partly on literature demonstrating the prognostic value of GA area on visual function.
- evidence from **the pivotal studies showing** at least a **positive trend of treatment** on secondary visual function parameters - considered **imperative**
- justify the **clinical meaningfulness** of the treatment effect observed with functional endpoint
- studies should be of **sufficient duration** to assess function

Should be supported also by other functional endpoints

Area of active discussion; it is **recommended to seek advice for trials and potential endpoints**

Interactions with regulators

- Early interaction is important
- Research, plan, and discuss options with regulators

Scientific Advice for trial plans

Qualification Advice for developed endpoints

Scientific advice (protocol assistance/rare diseases);

Qualification advice and opinion for novel methods

Interaction with regulators

Scientific Advice

- Procedure
  - Submission of a Briefing Document with all relevant information (interaction with EMA)
  - Assignment of Coordinators
  - Review by SAWP Coordinators and potential List of Questions
  - Potential Discussion Meeting

- Scientific Advice procedure outcomes:
  - Final advice letter with answers to the posed questions

Interaction with regulators

Qualification Procedure

- Procedure
  - Submission of a Briefing Document with all relevant information (interaction with EMA)
  - Assignment of Coordinators and *Qualification Team*
  - Review by SAWP Coordinators/QT and List of Questions
  - *Discussion Meeting with Qualification Team*
  - *Potential additional LoI and Meetings between Qualification Team and Applicant*

- Qualification procedure outcomes:
  - Qualification Advice
  - *Letter of Support*
  - *Qualification Opinion*

Austrian Agency for Health
and Food Safety

Thank you

Pictures: Christina Fink, Asvola, Monkey Business Images, malshkoff/Shutterstock.com