BEAT CF

PATIENT DRIVEN EVIDENCE

Designing clinical trials using causal models

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Some facts about cystic fibrosis

Cystic Fibrosis (CF) is a genetic disease affecting major organs including the lungs and pancreas

1 in 4 people with a CF-related lung exacerbation will not return to their previous lung function

CF affects a person's ability to clear their airway, allowing bacteria and viral infections to settle in the lungs and airways

The average person will be admitted to hospital once per year to manage a lung exacerbation

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Separation of evidence creation and decision-making

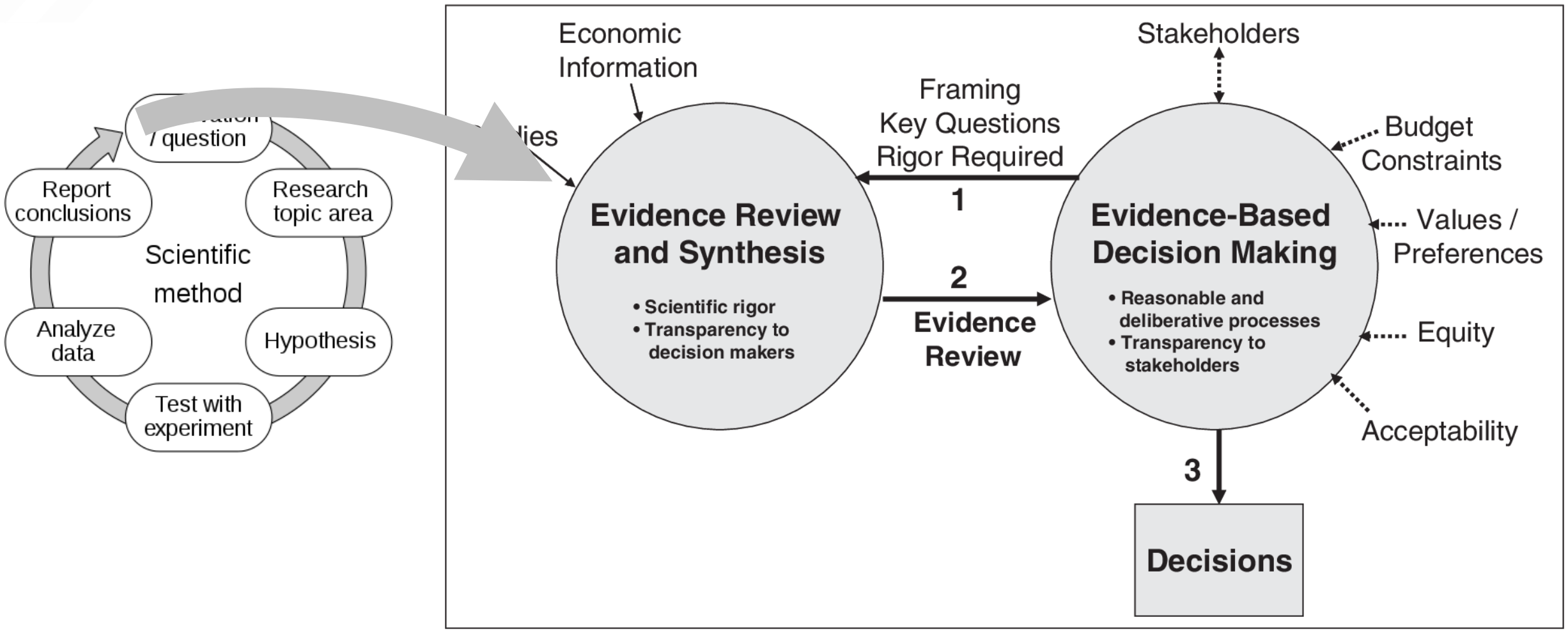

Figure 1 Dynamic relationship between evidence review and synthesis and evidence-based decision making.

https://en.wikipedia.org/wiki/Scientific_method

Teutsch; MedDesMak 2005

Designing studies that are reactive to decision-making

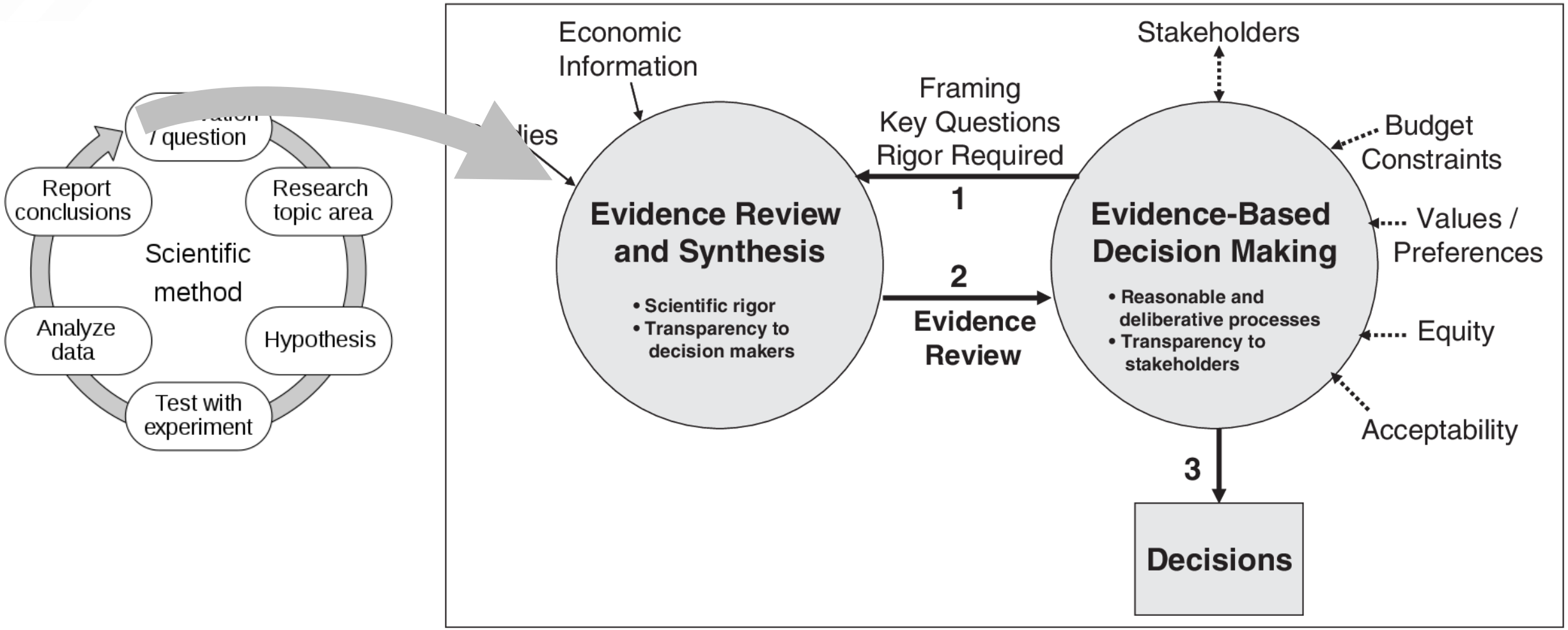

Figure 1 Dynamic relationship between evidence review and synthesis and evidence-based decision making.

https://en.wikipedia.org/wiki/Scientific_method

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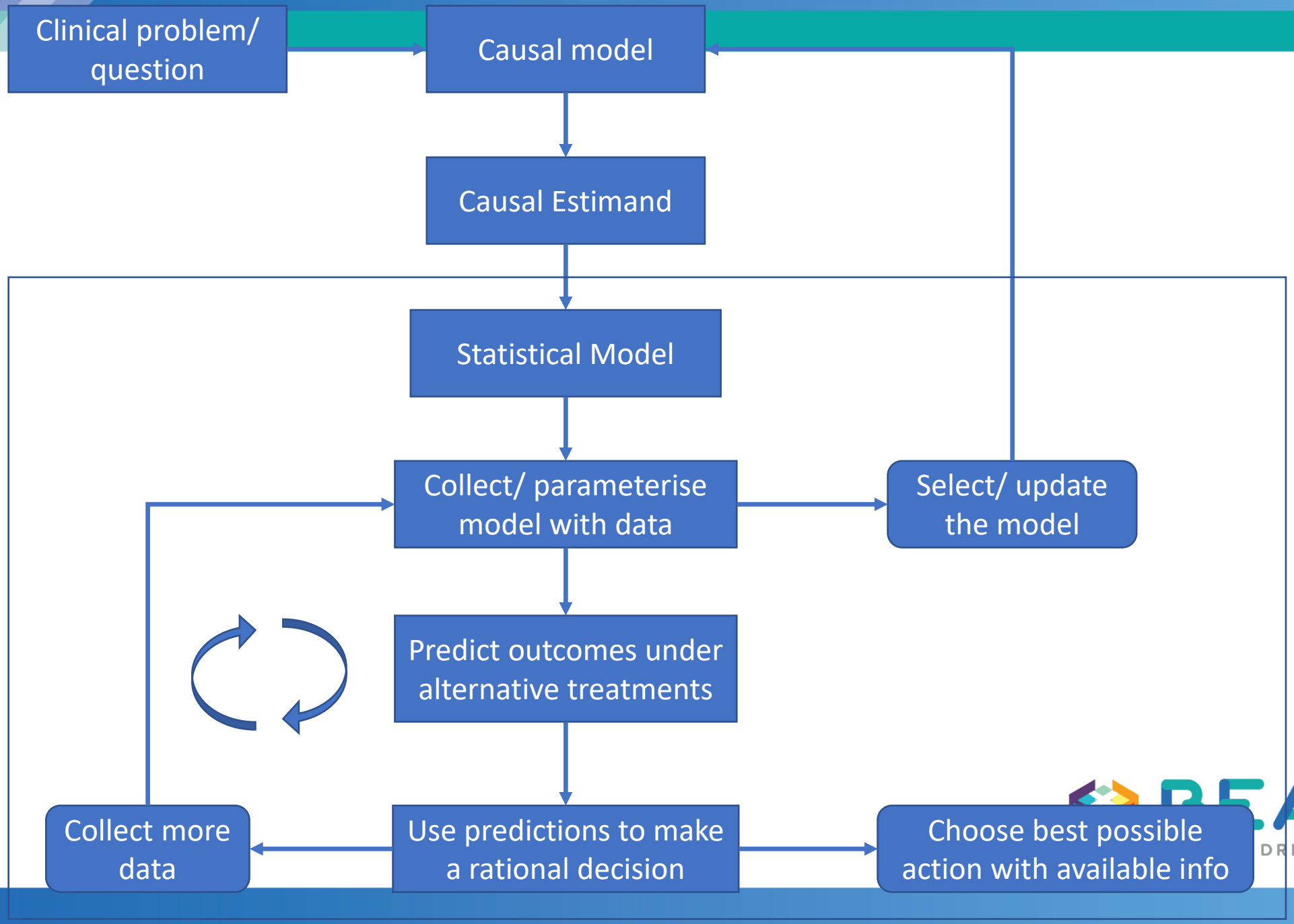
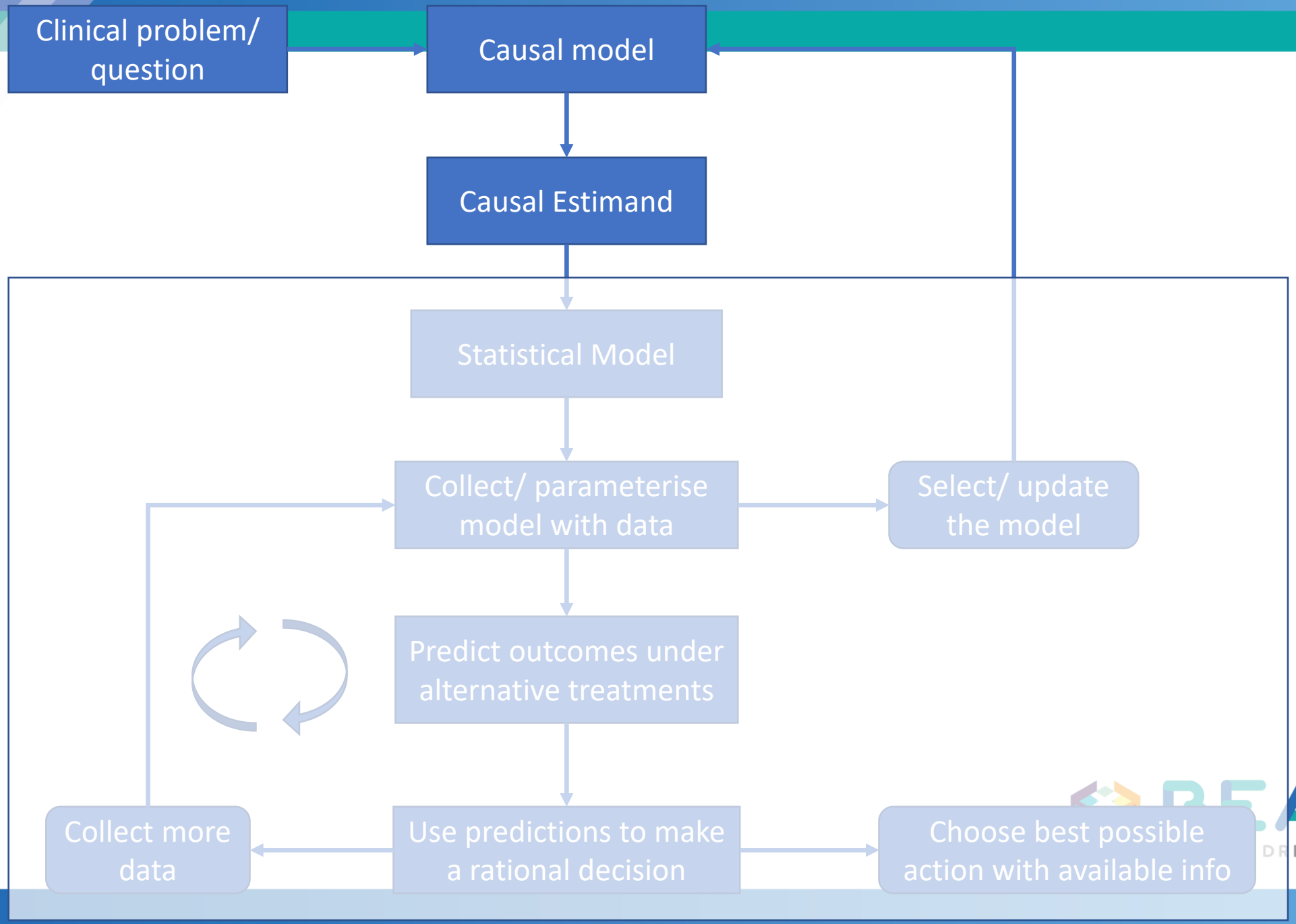

Clinical problem/ question
Causal model
Causal Estimand
Statistical Model
Collect/ parameterise model with data
Select/ update the model
Predict outcomes under alternative treatments
Collect more data
Use predictions to make a rational decision
Choose best possible action with available info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Clinical problem/ question

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1. Stating the clinical question

Broadly, what (and whose) clinical **decision/ action** do we wish to inform?

- How **should** pulmonary exacerbations of CF be managed?
- Which antibiotics? What dose? What frequency? What duration? What route of administration **should** be prescribed?
- When **should/can** inhaled antibiotics be used? At what dose, frequency and duration?
- Which adjunctive therapies **should** be used?
- How **should** chest physiotherapy be delivered?

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Clinical problem/ question → Causal model

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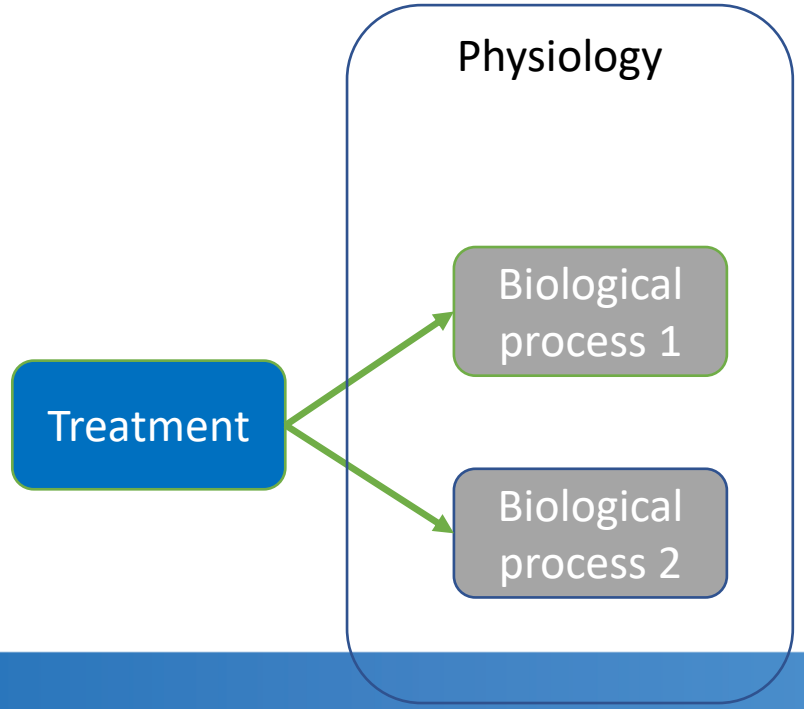
2. Formulate a causal model of the clinical problem



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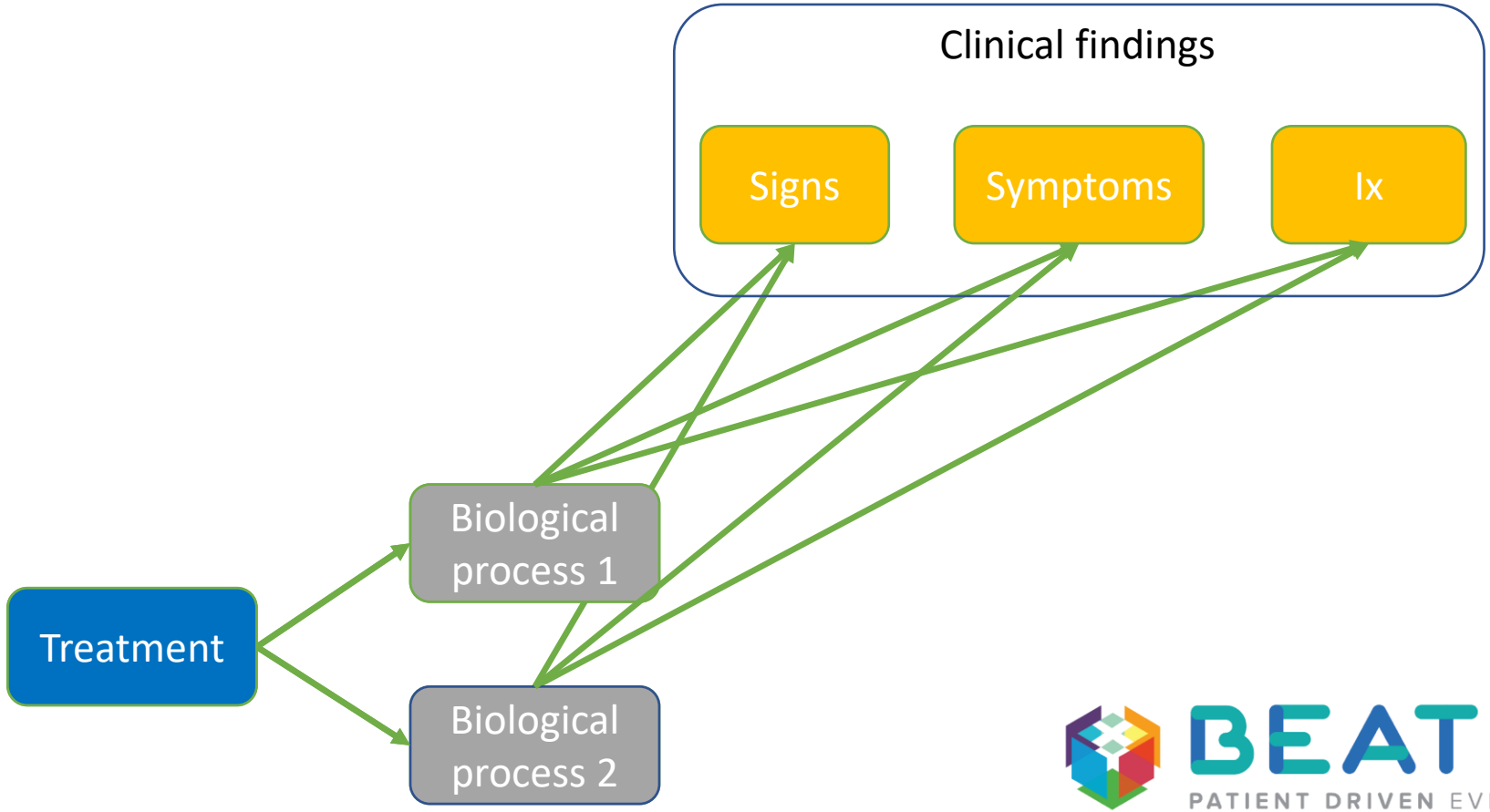

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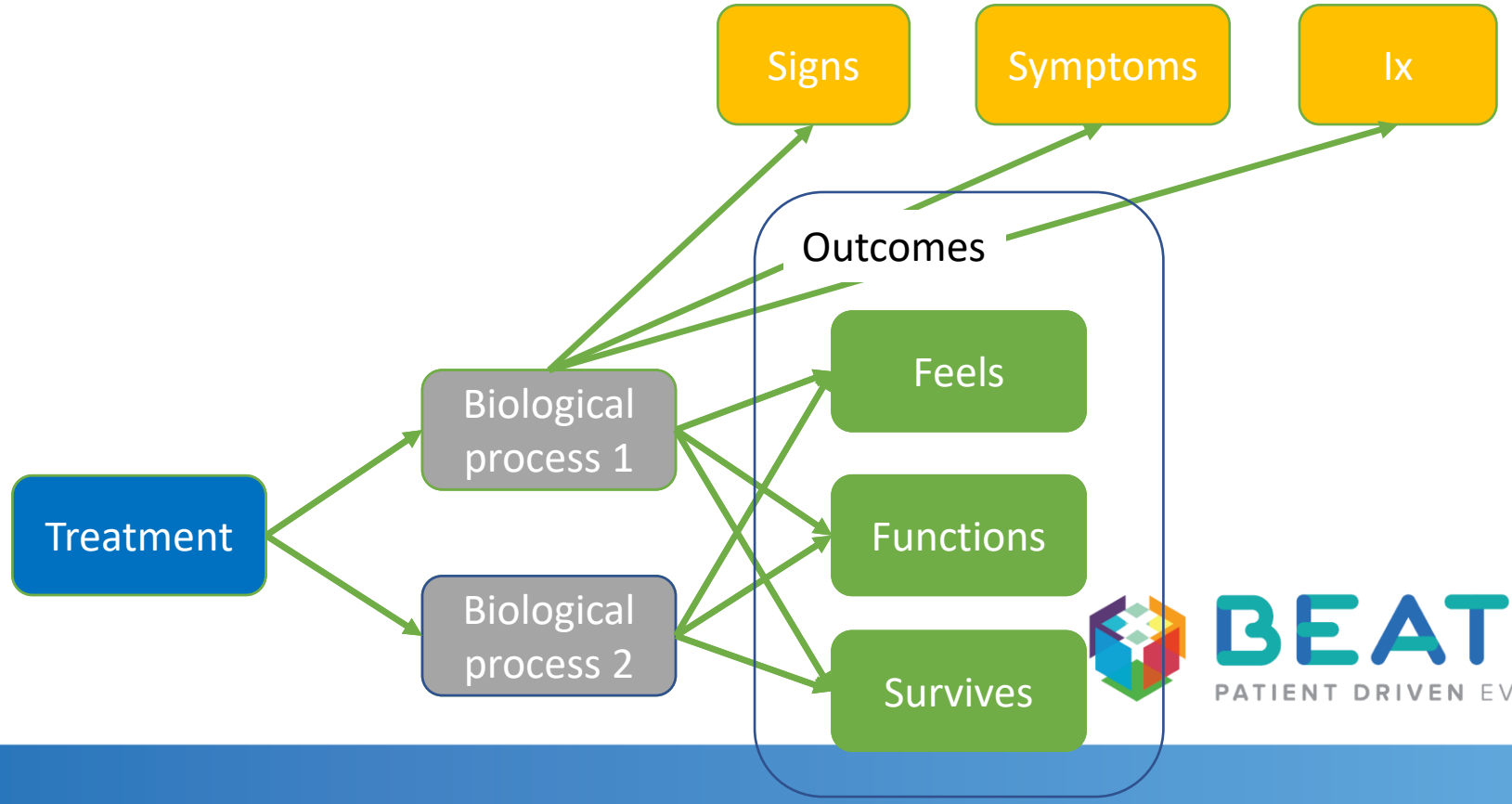

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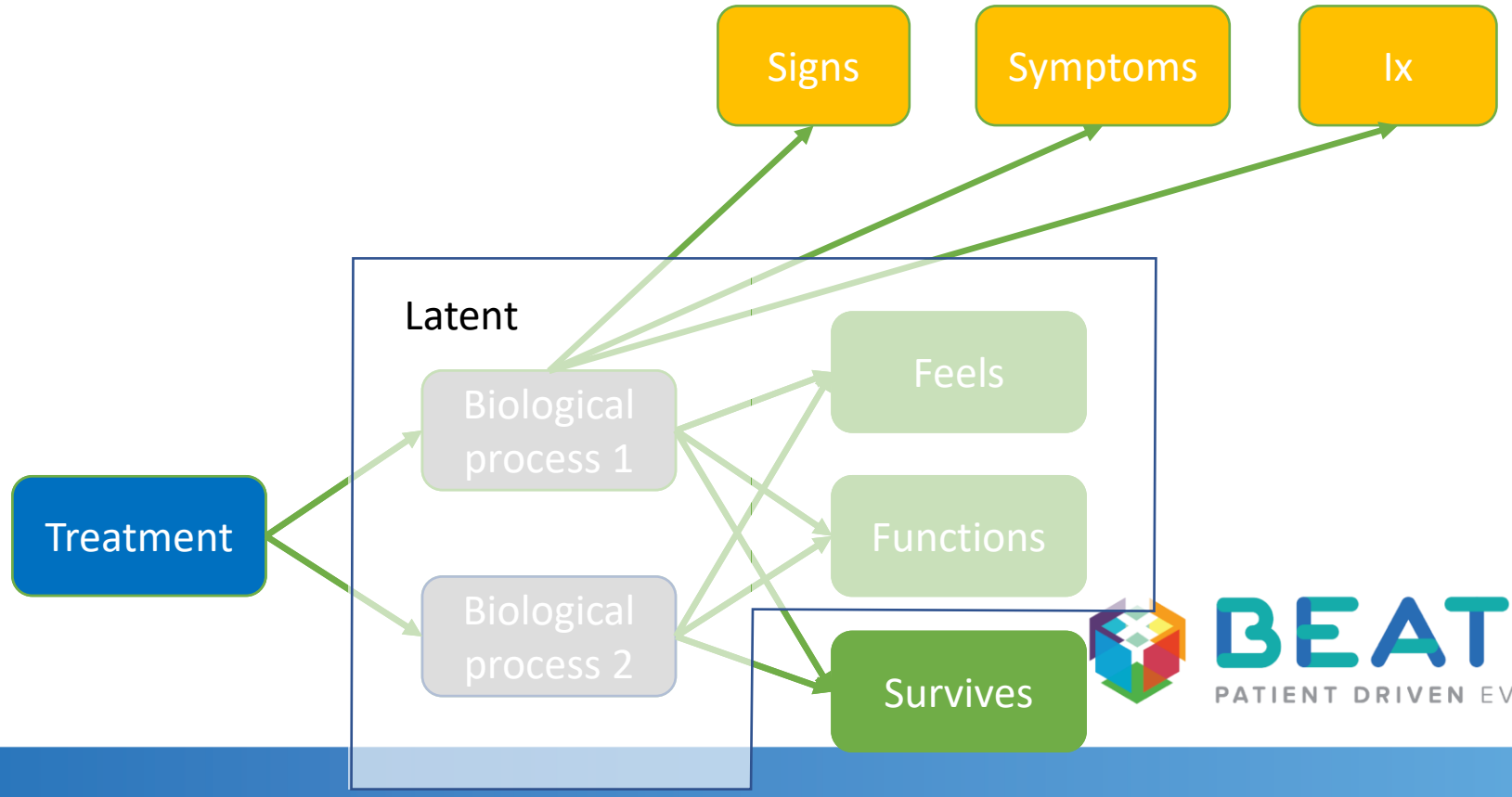

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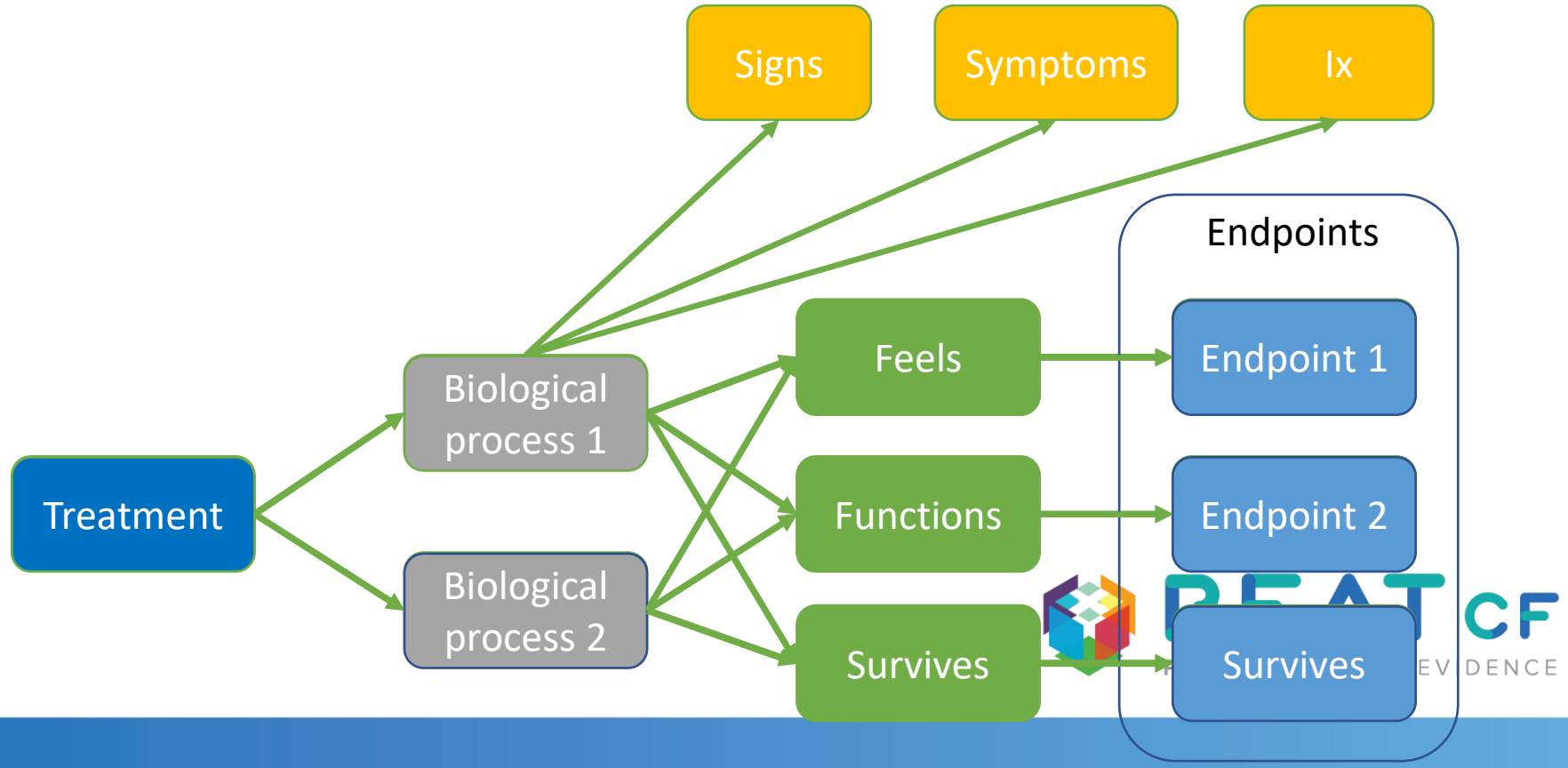

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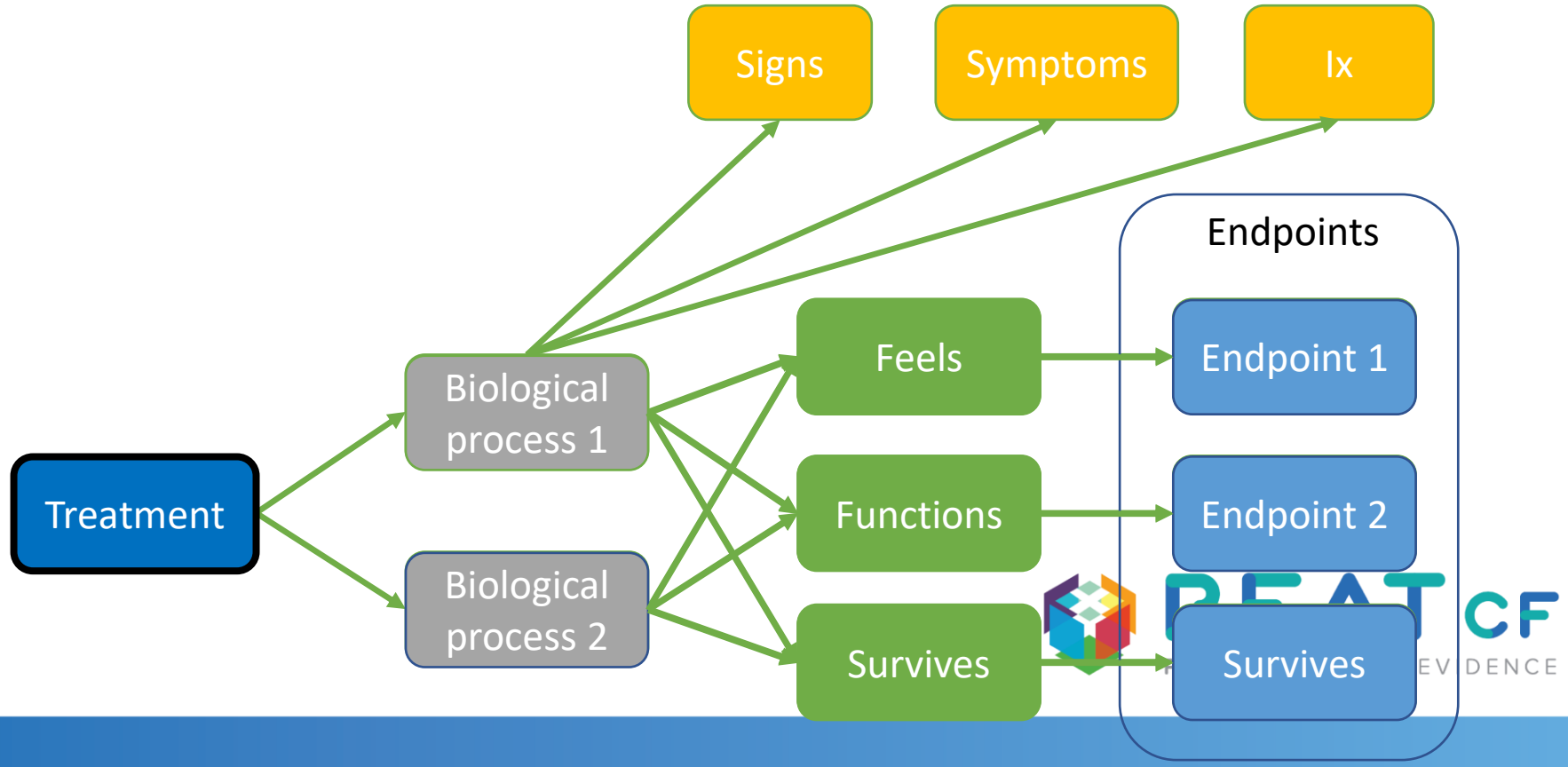

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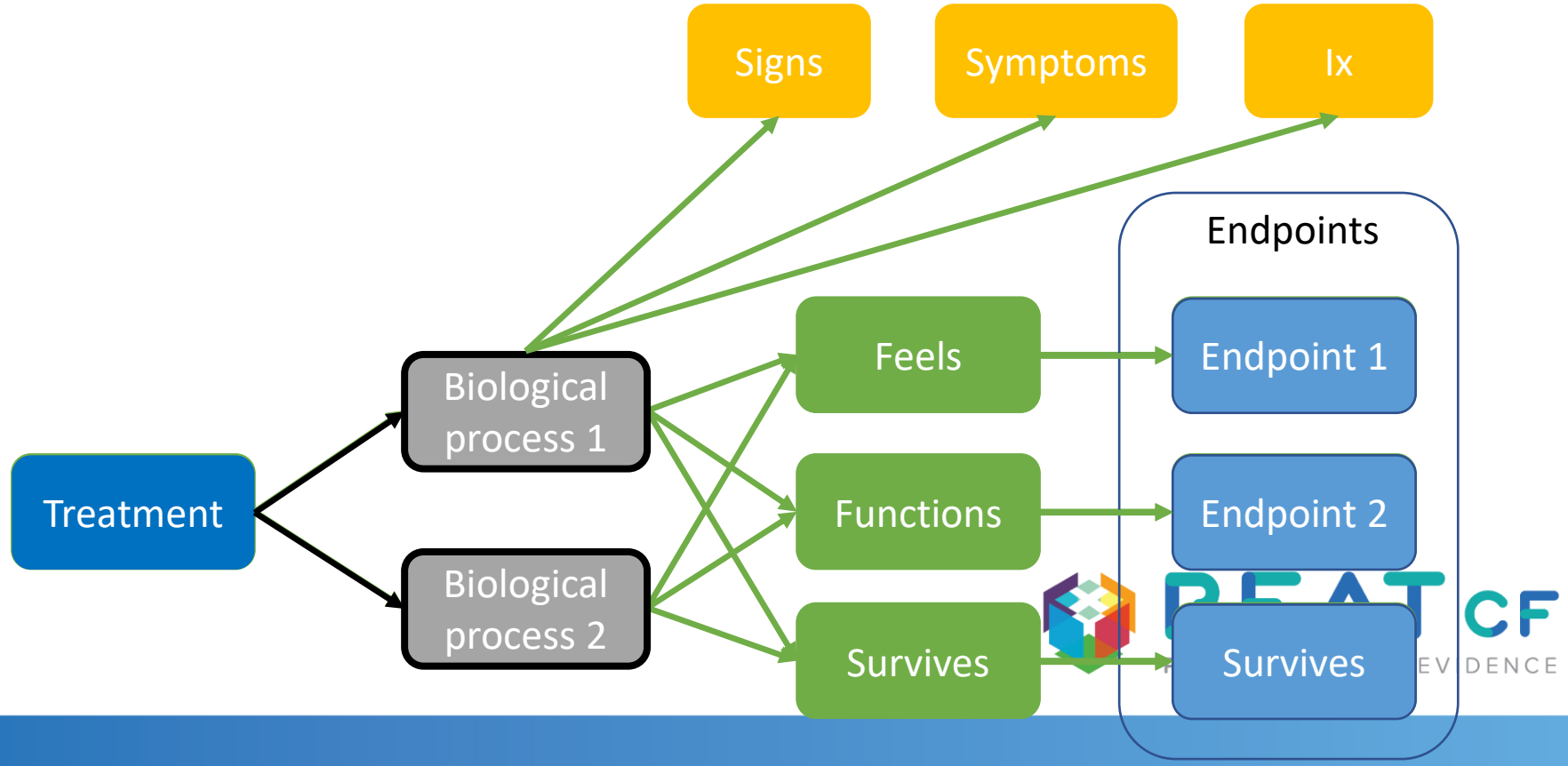

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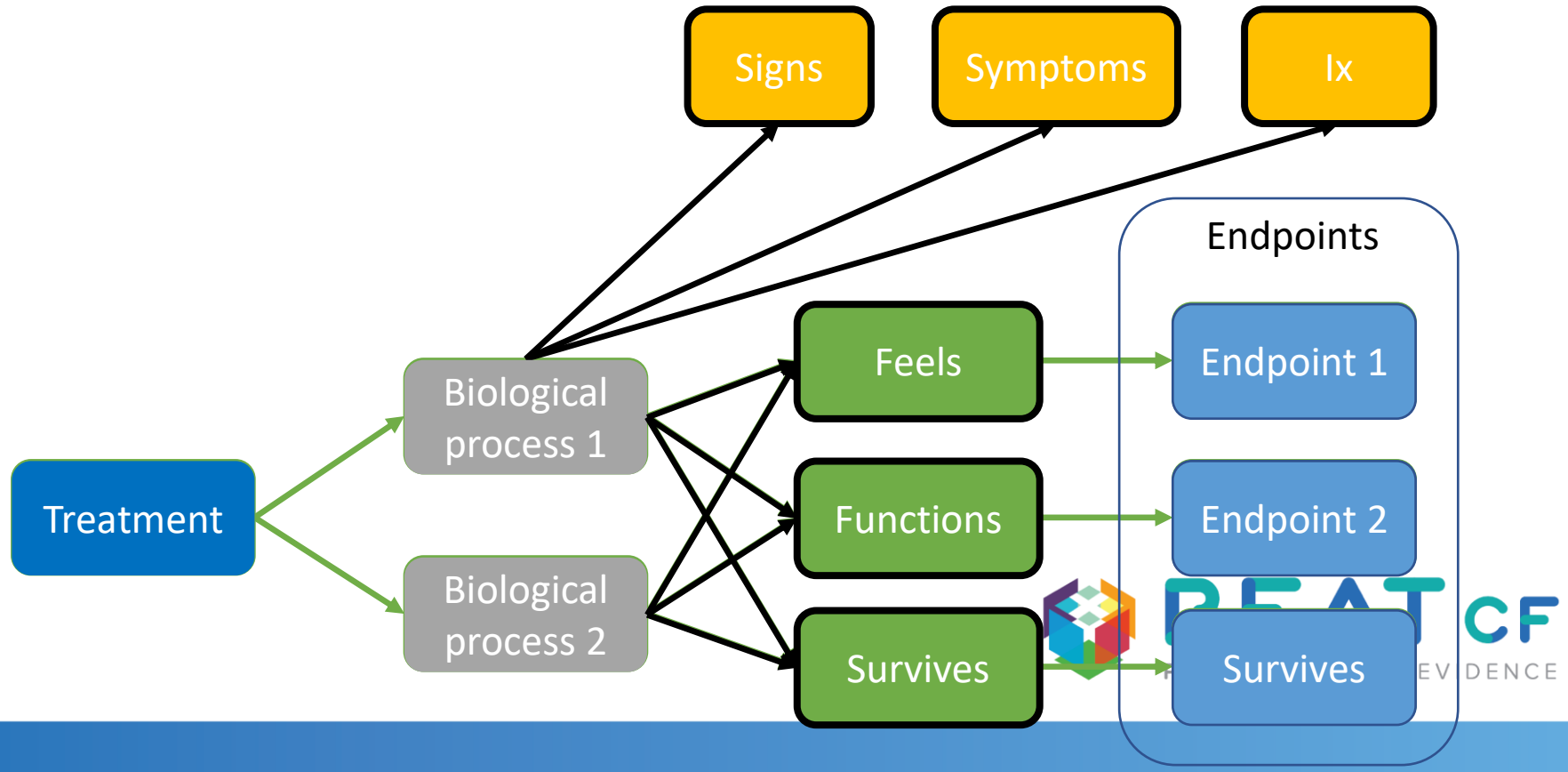

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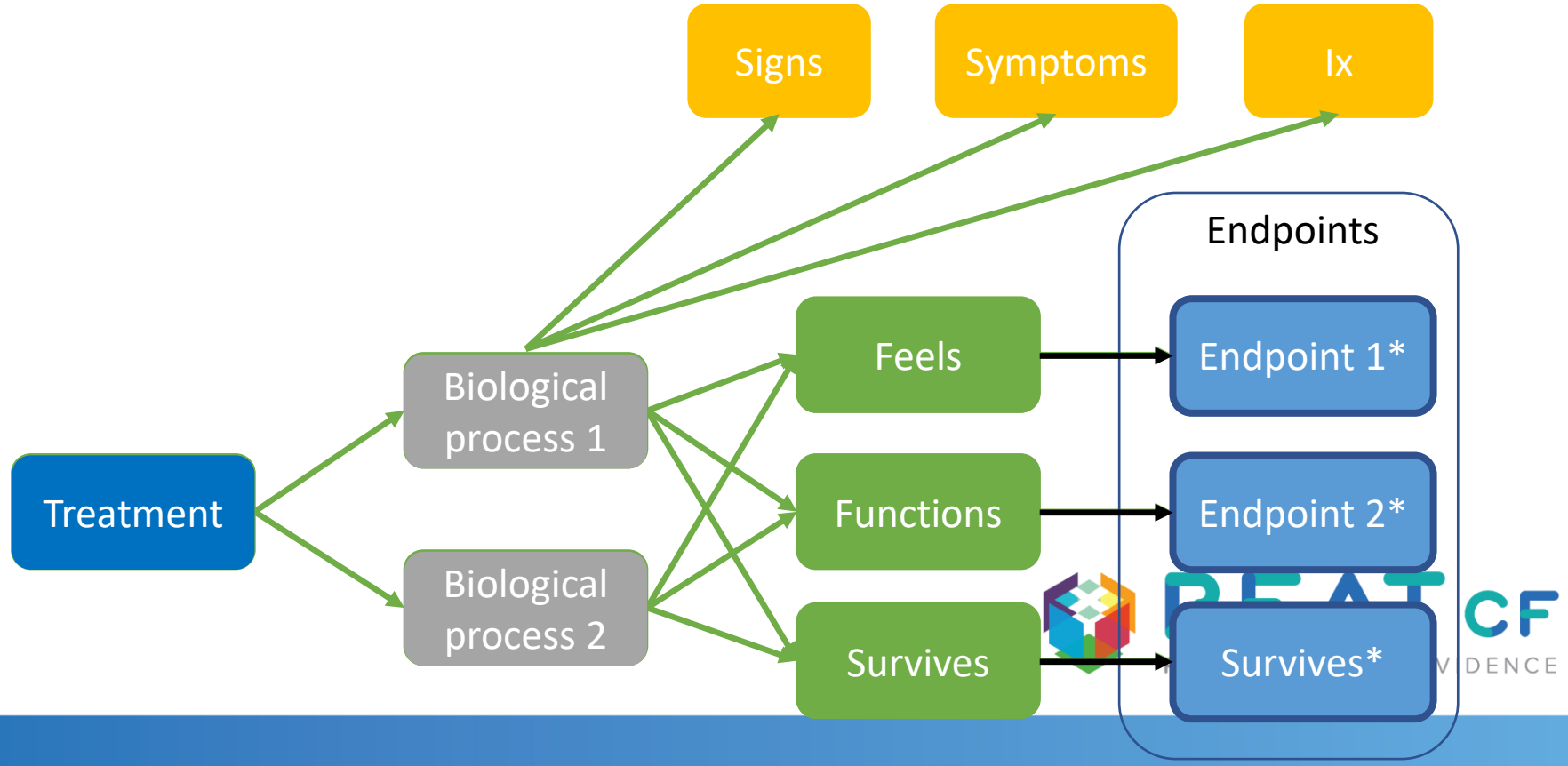

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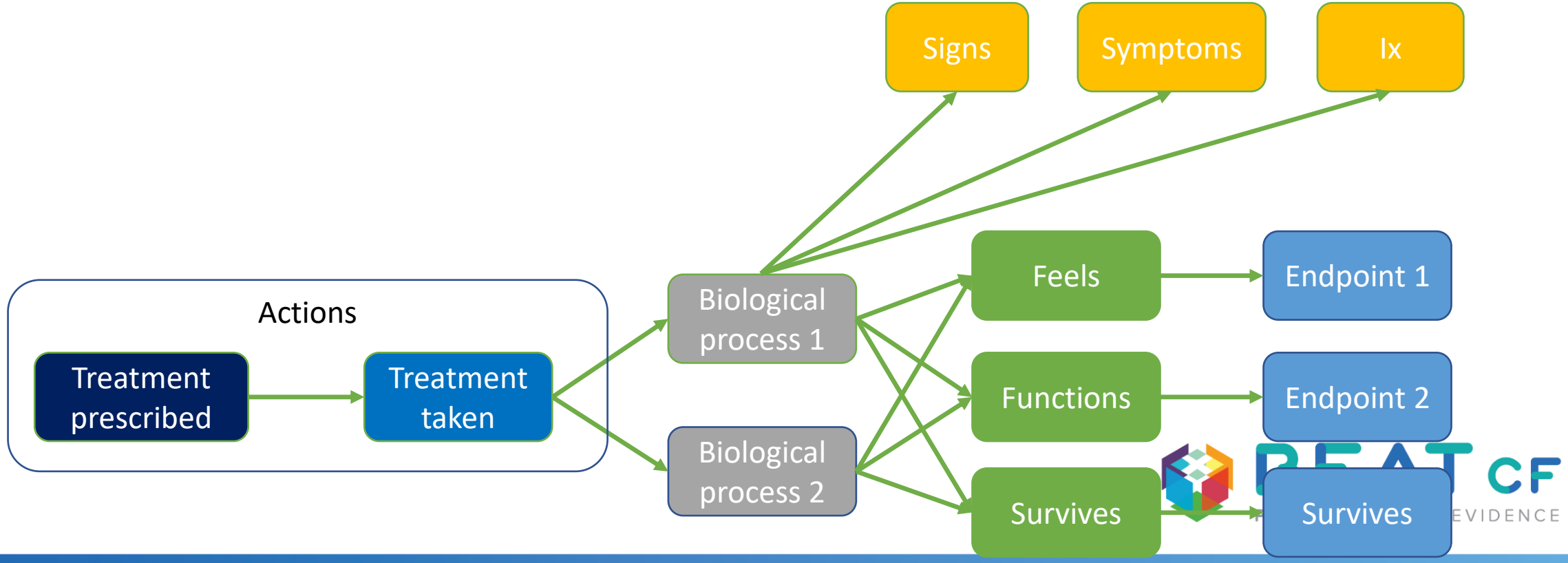

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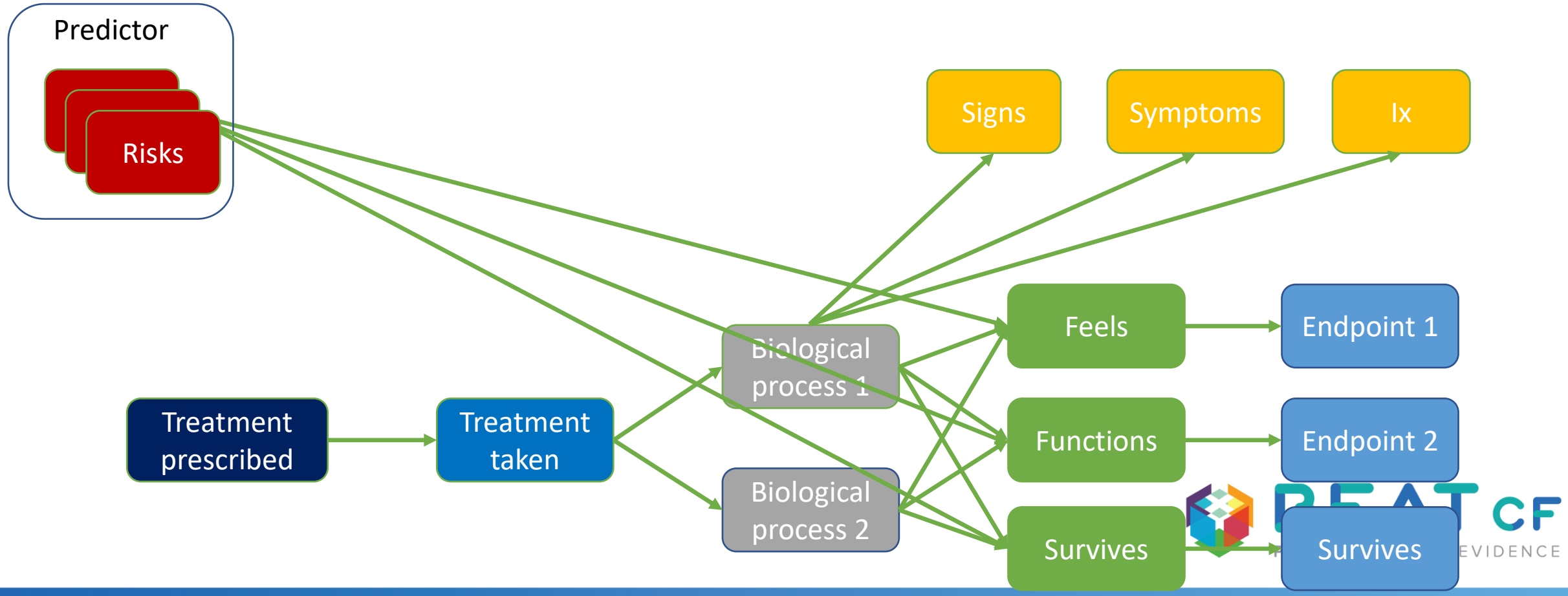

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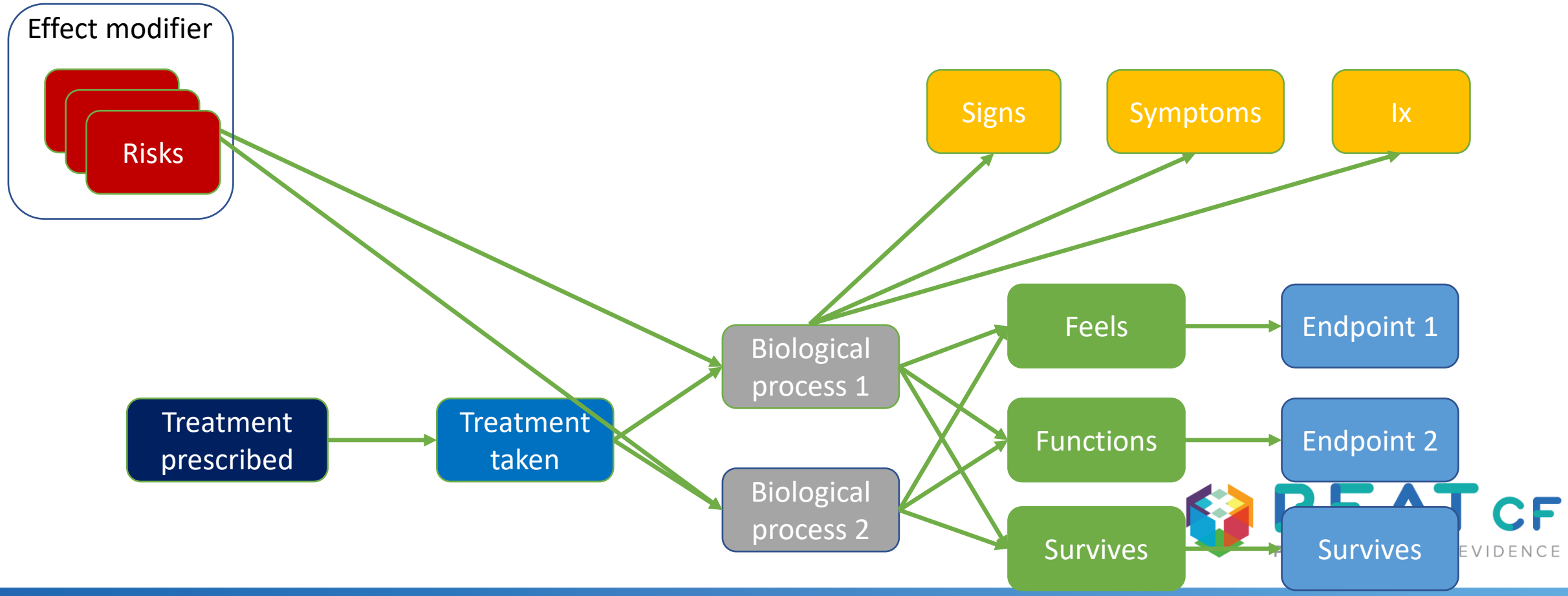

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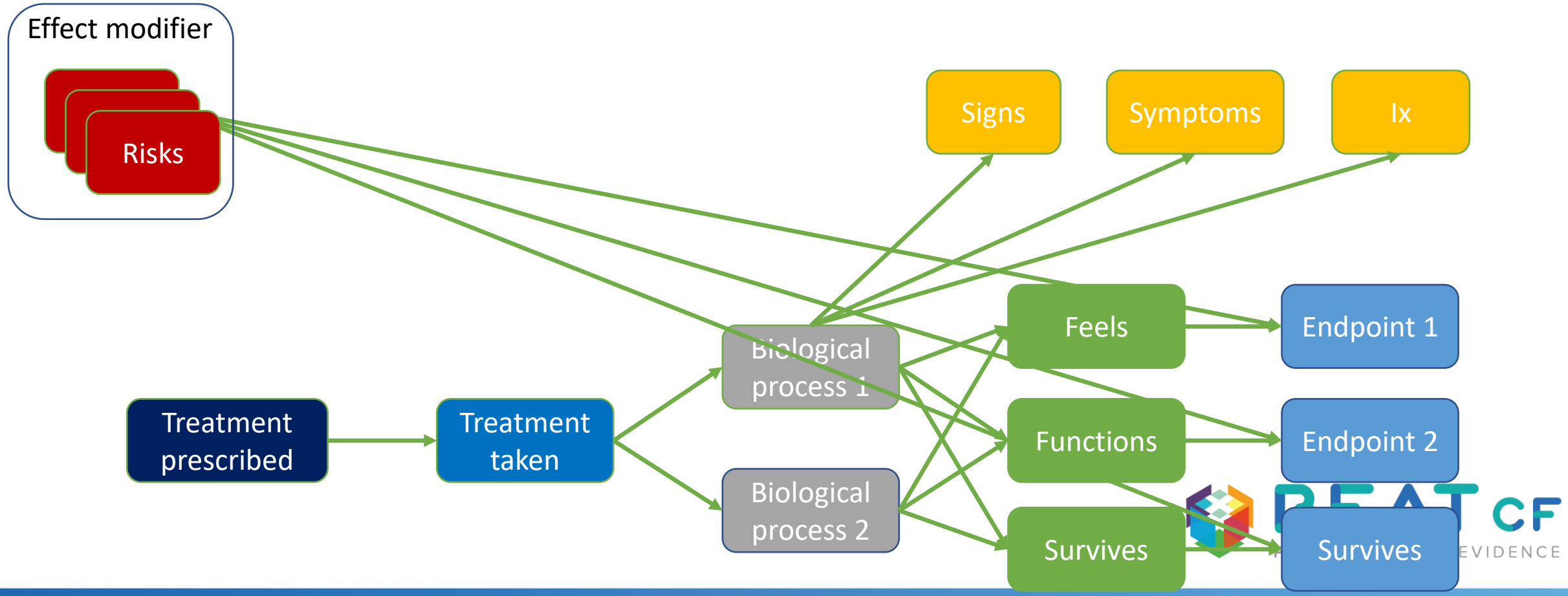

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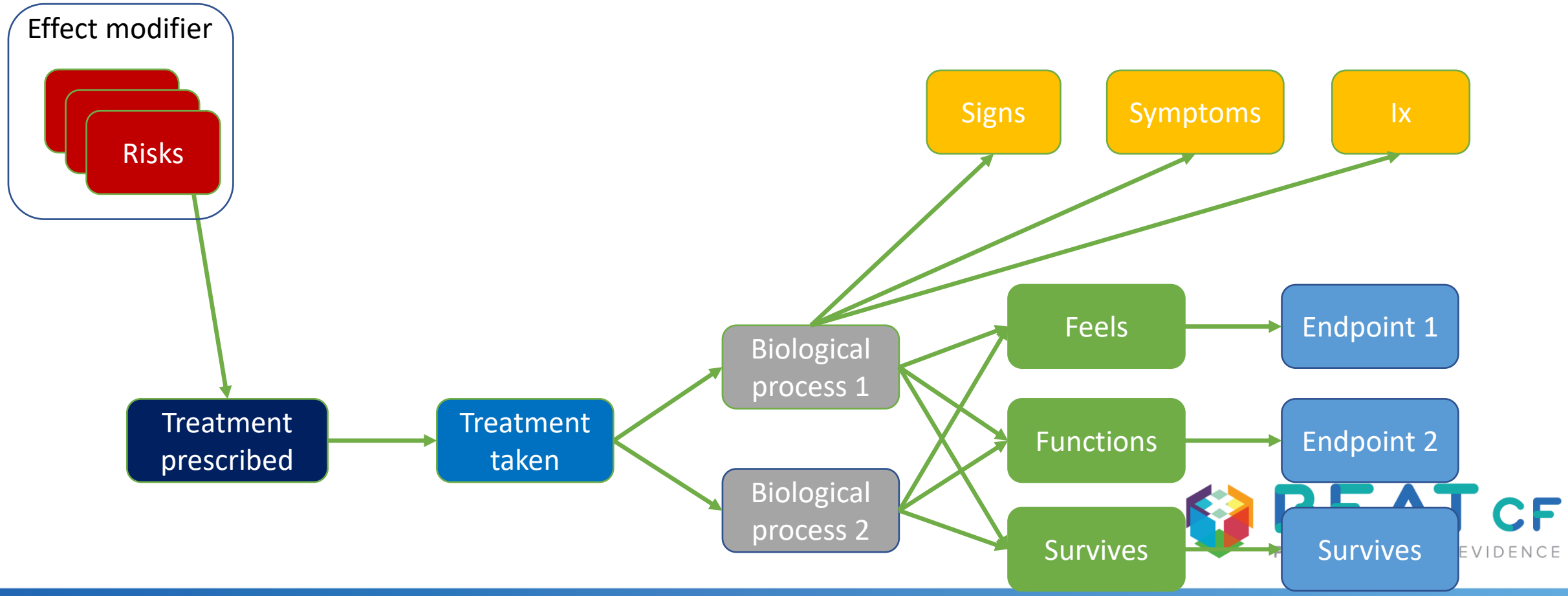

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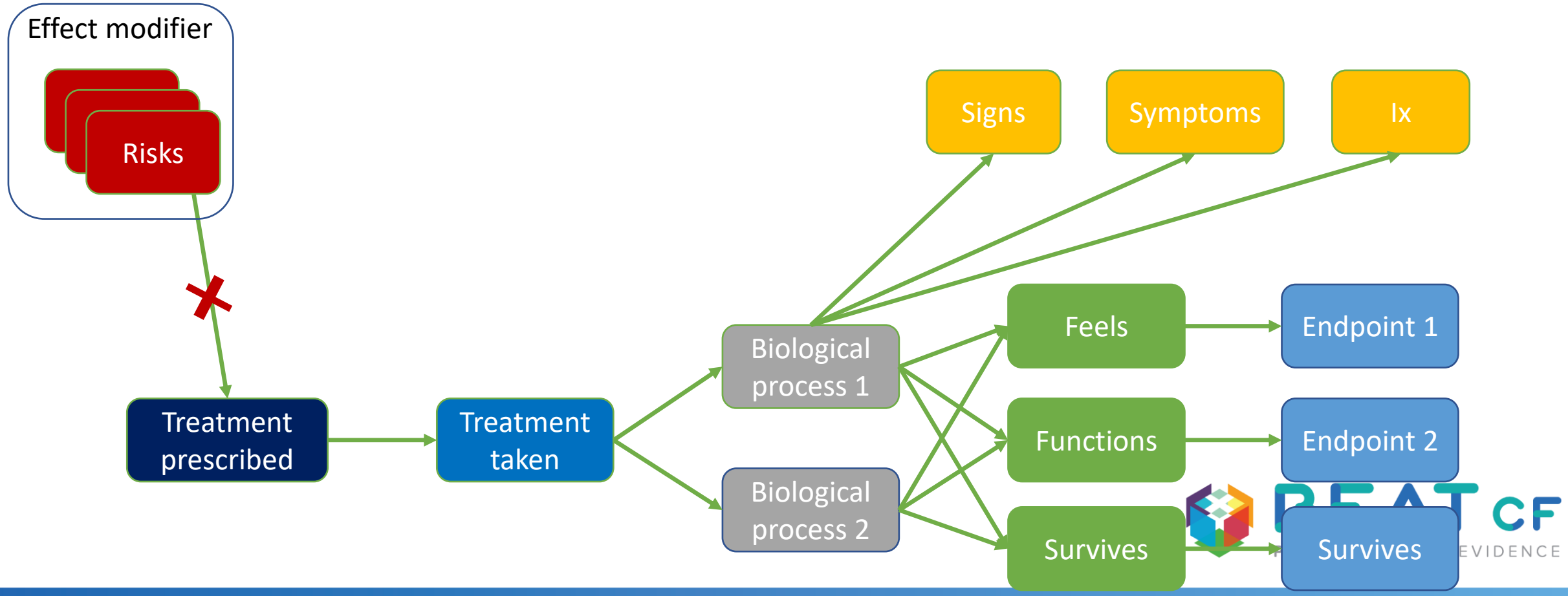

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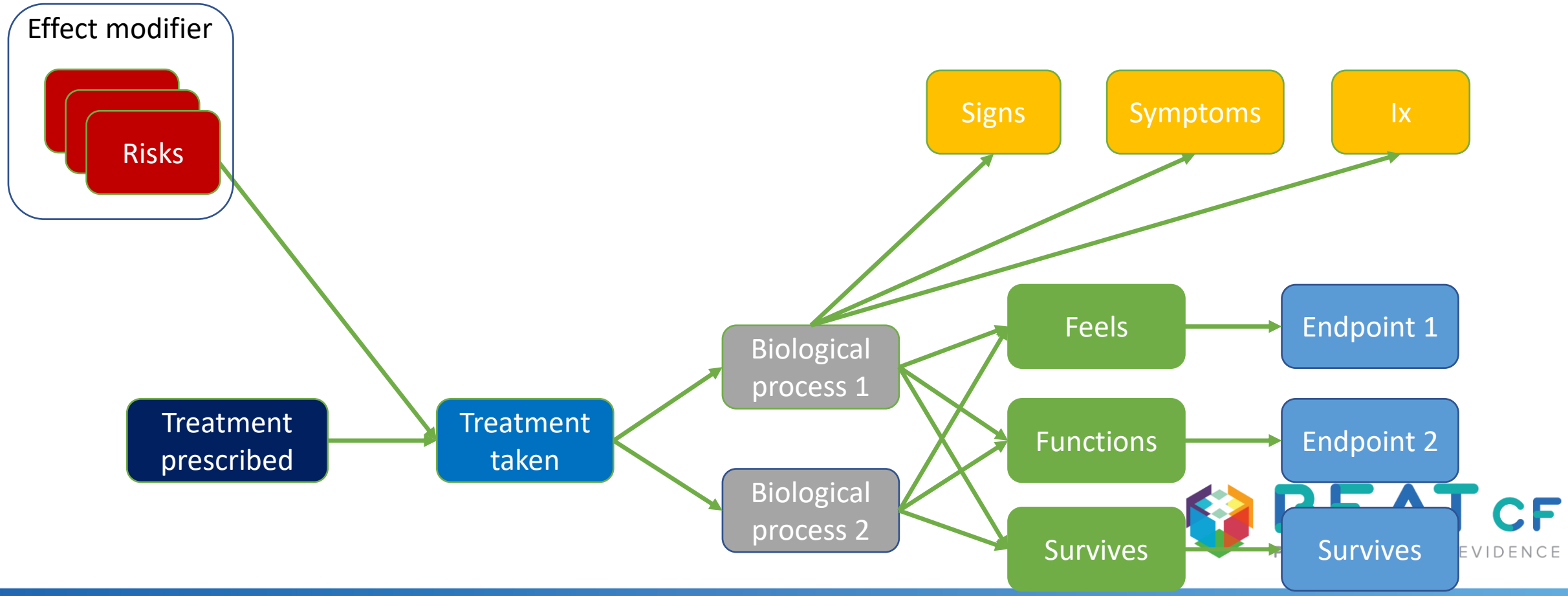

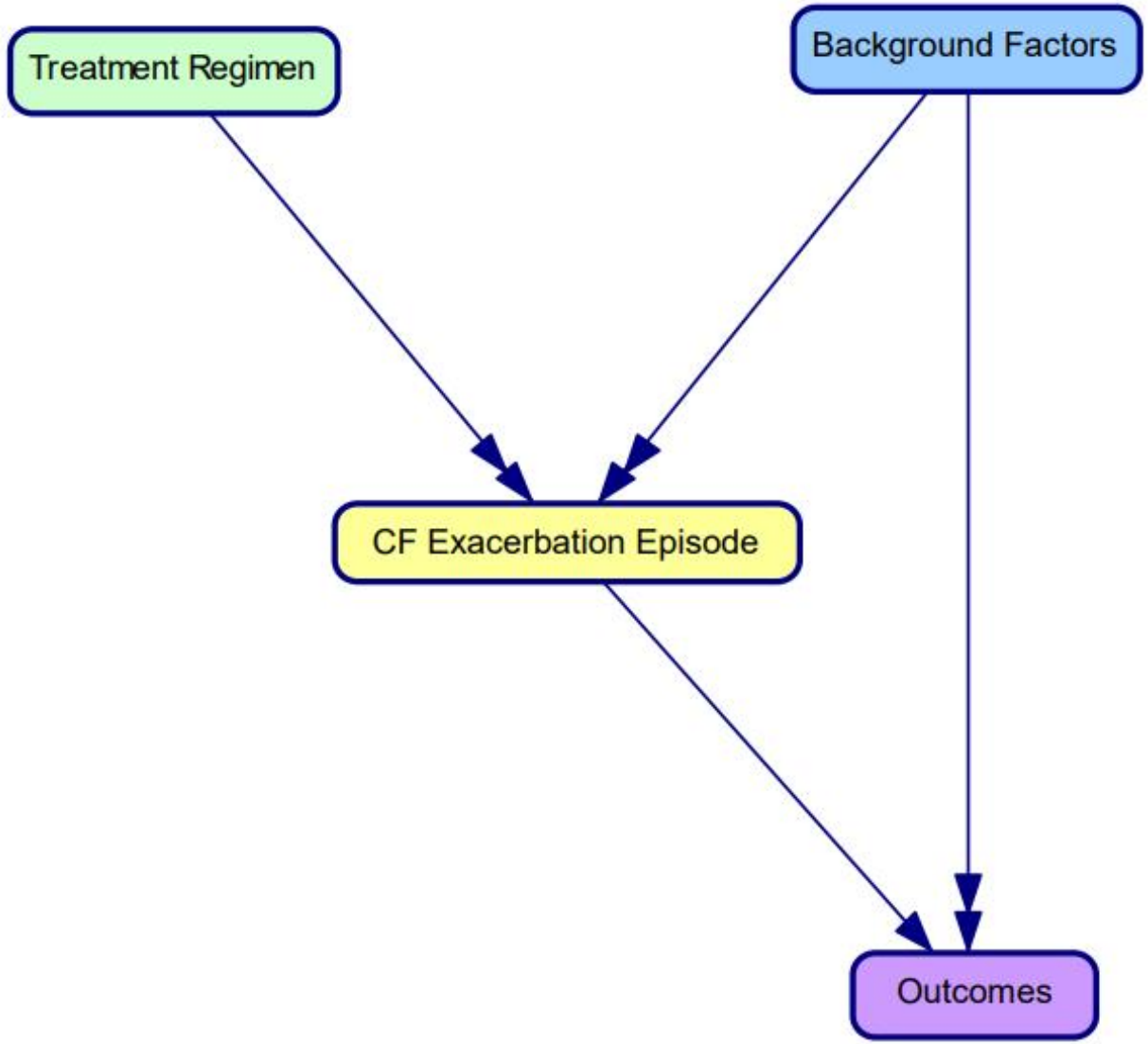

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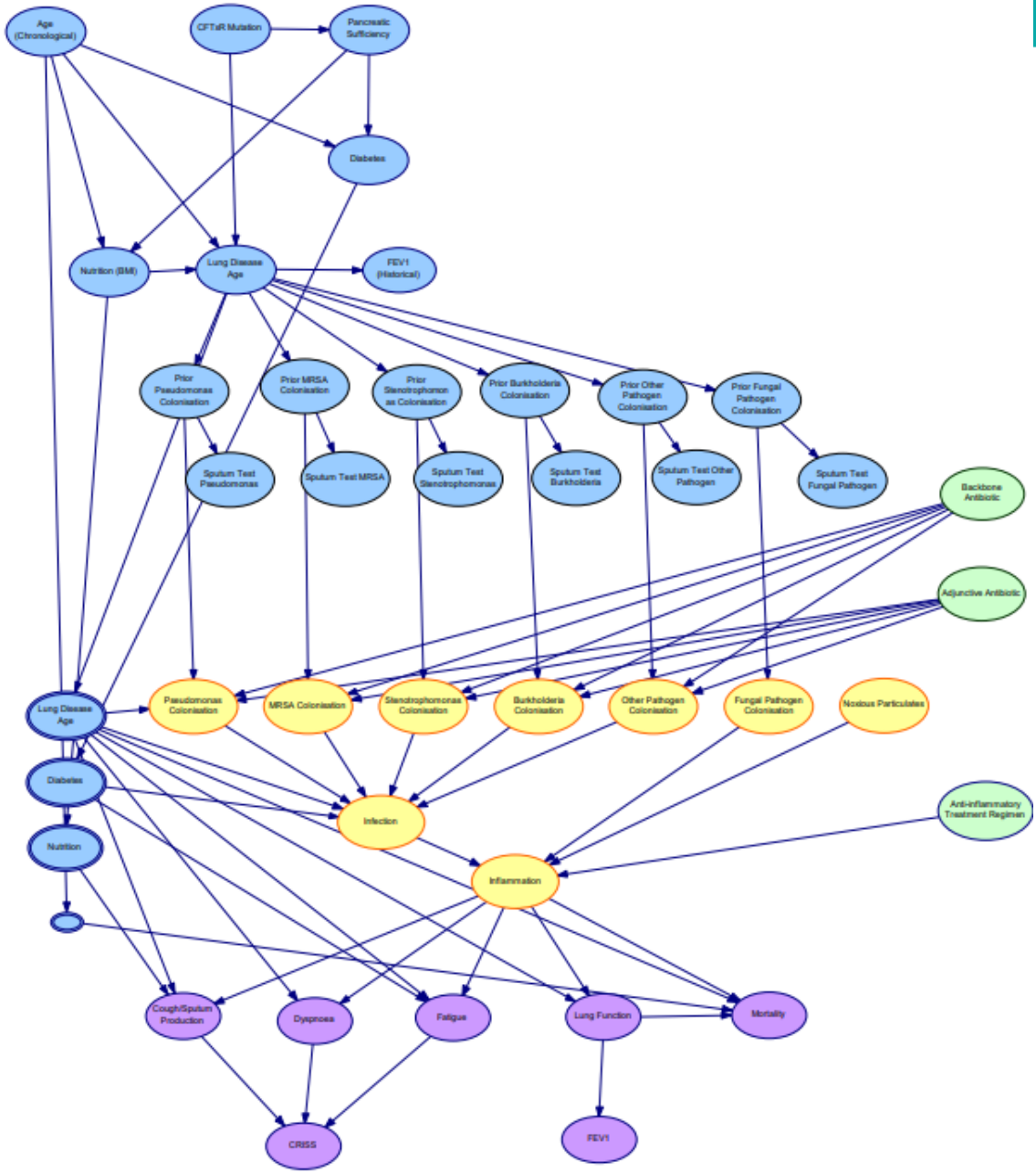

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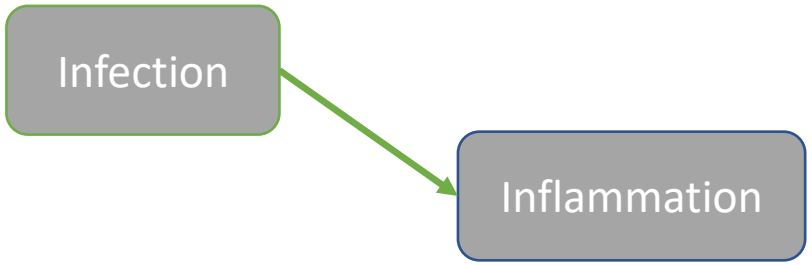

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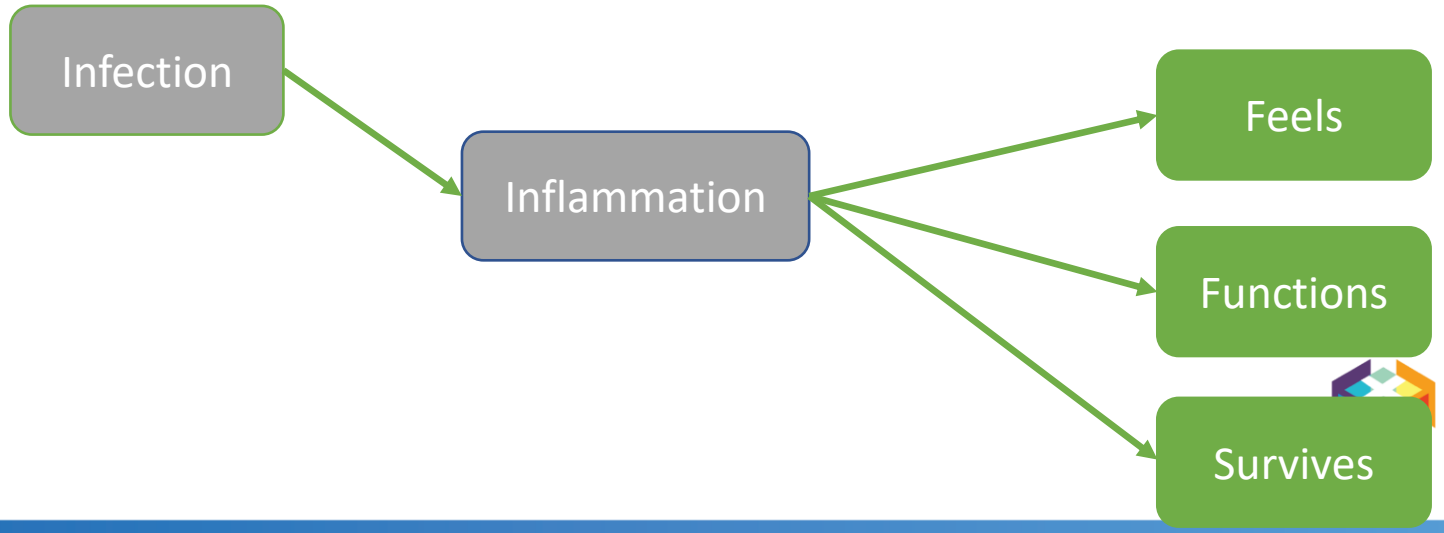

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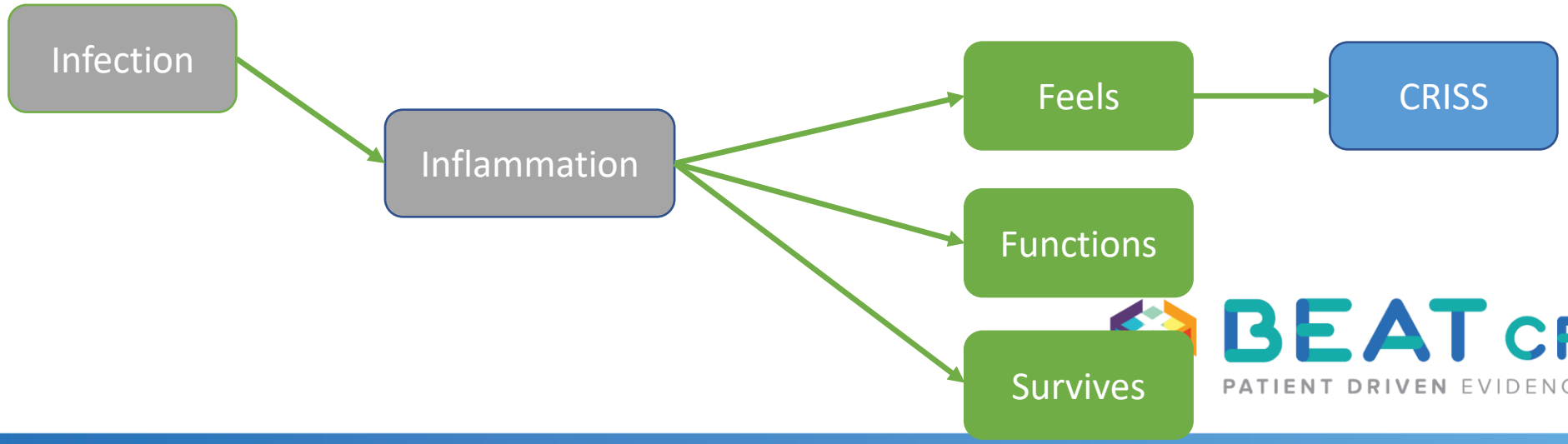

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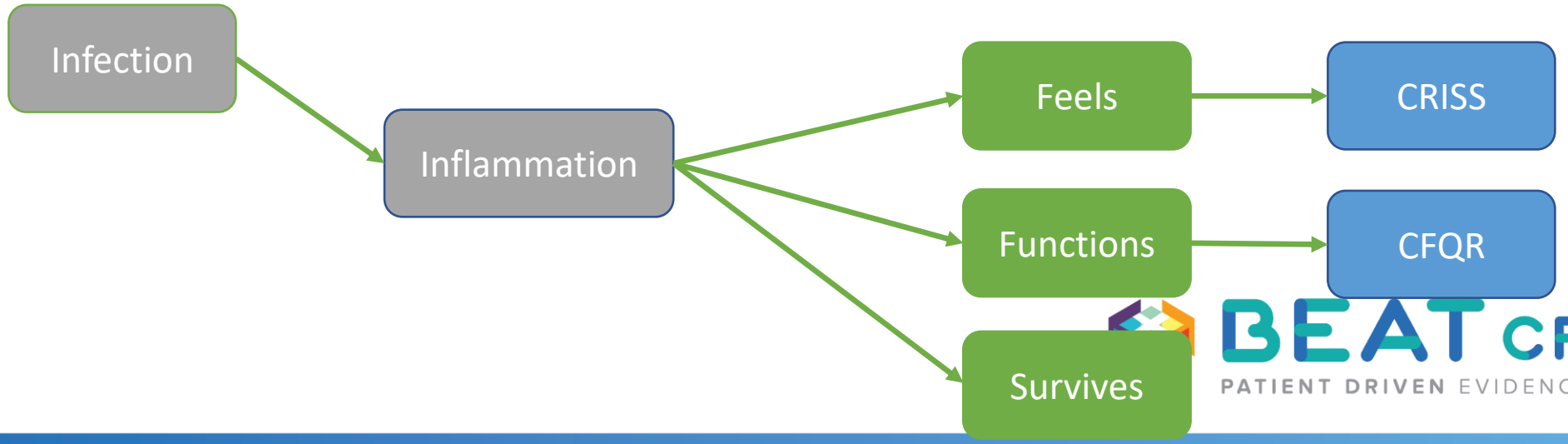

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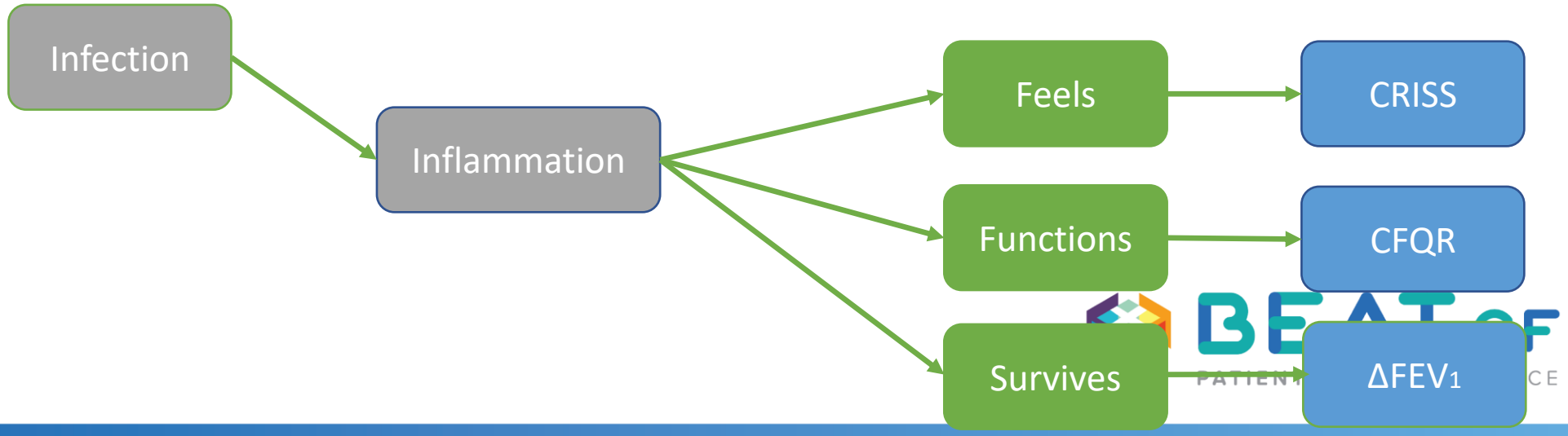

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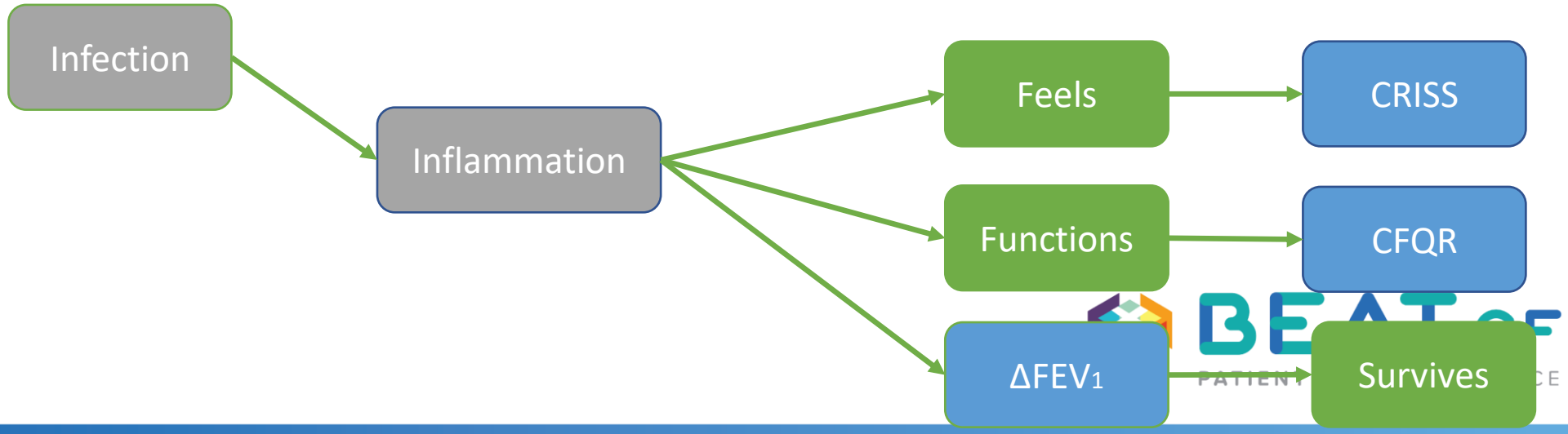

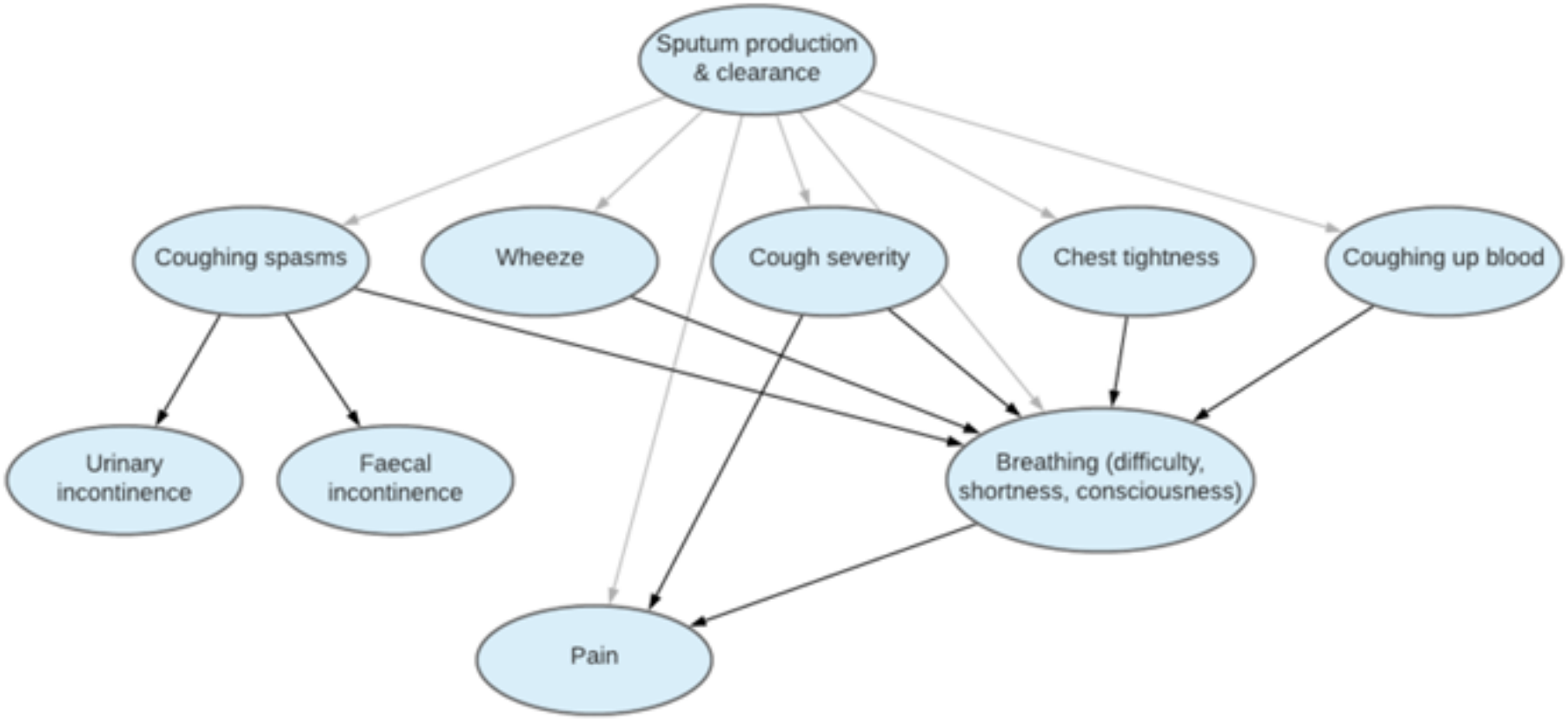

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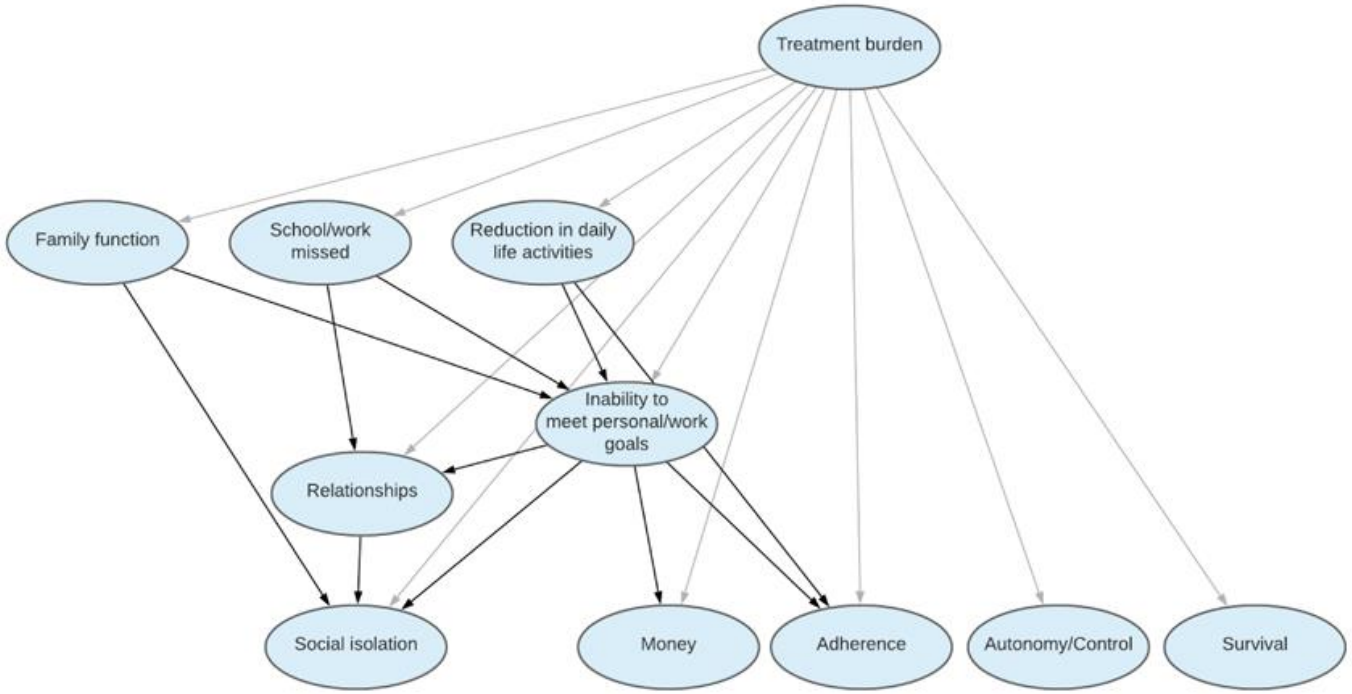
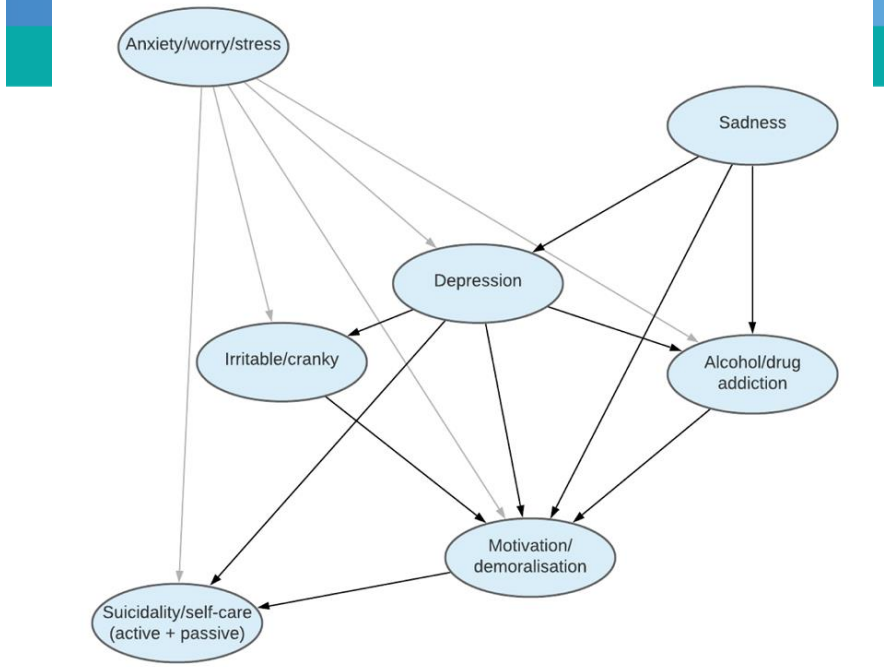
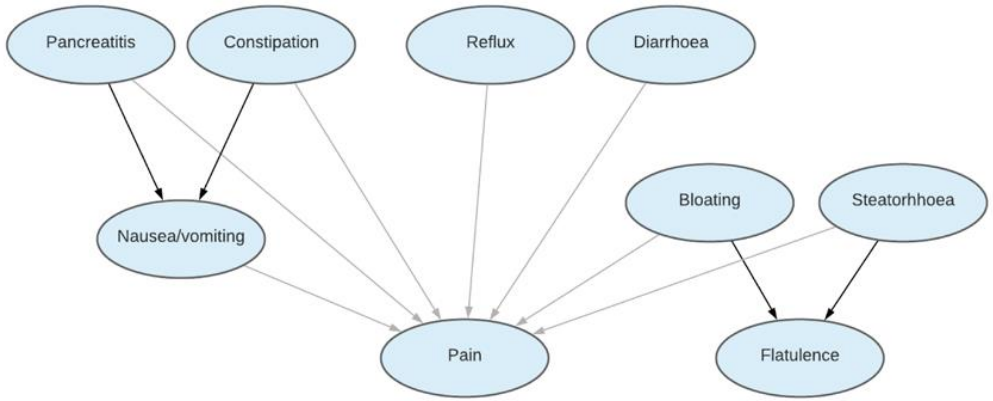
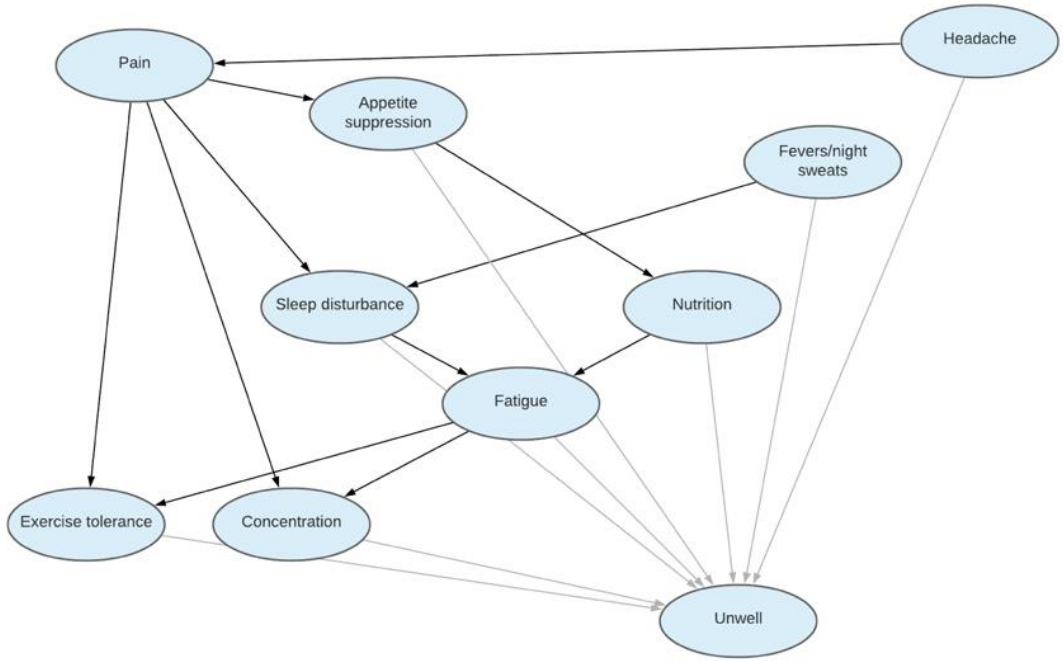
McLeod C, et al. BMJ Open Resp Res 2021


Treatment burden
Family function
School/work missed
Reduction in daily life activities
Inability to meet personal/work goals
Relationships
Social isolation
Money
Adherence
Autonomy/Control
Survival


Anxiety/worry/stress
Sadness
Depression
Irritable/cranky
Alcohol/drug addiction
Motivation/ demoralisation
Suicidality/self-care (active + passive)


Pancreatitis
Constipation
Reflux
Diarrhoea
Bloating
Steatorhhoea
Nausea/vomiting
Pain
Flatulence


Pain
Headache
Appetite suppression
Fevers/night sweats
Sleep disturbance
Nutrition
Fatigue
Exercise tolerance
Concentration
Unwell

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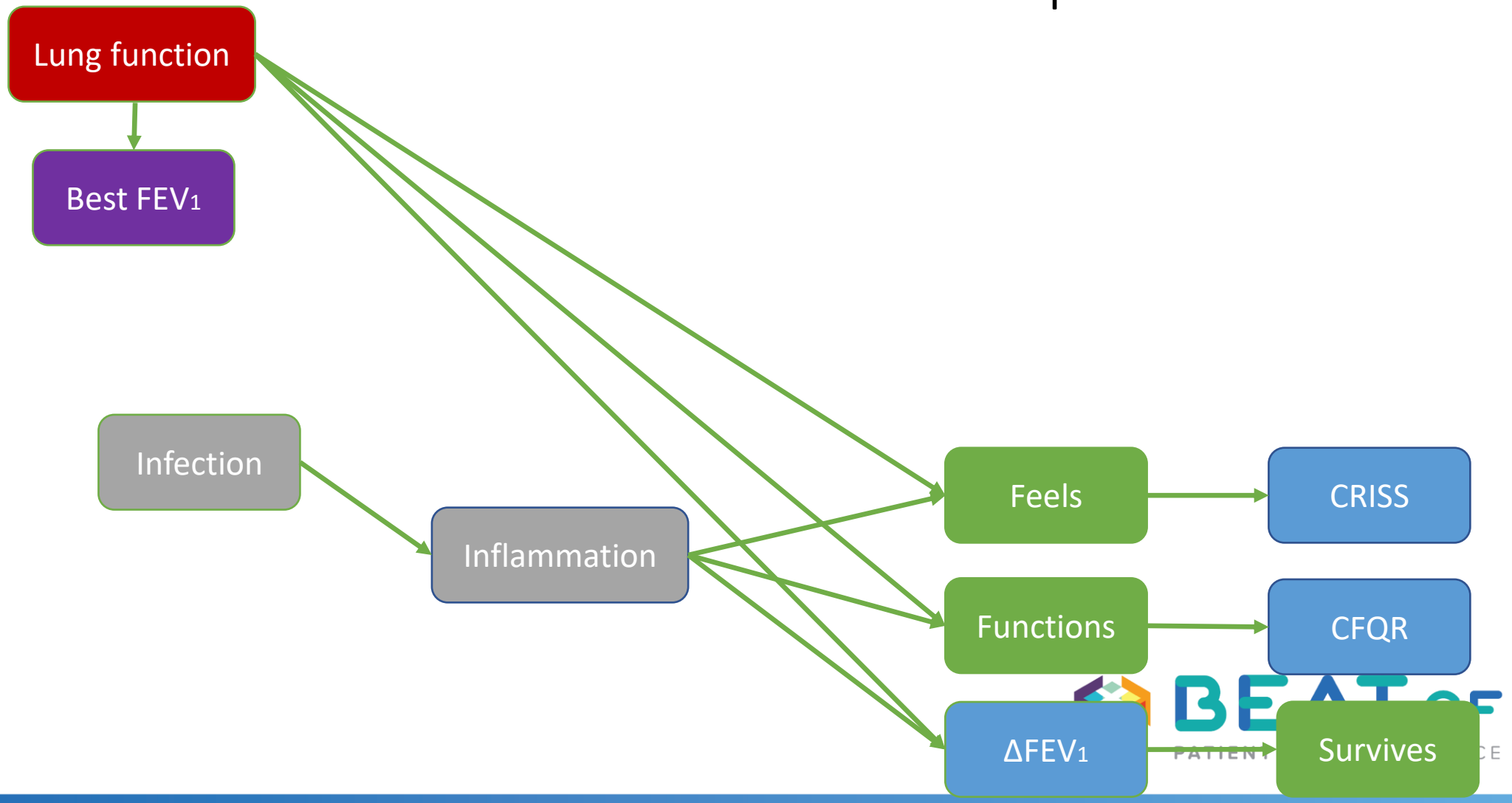

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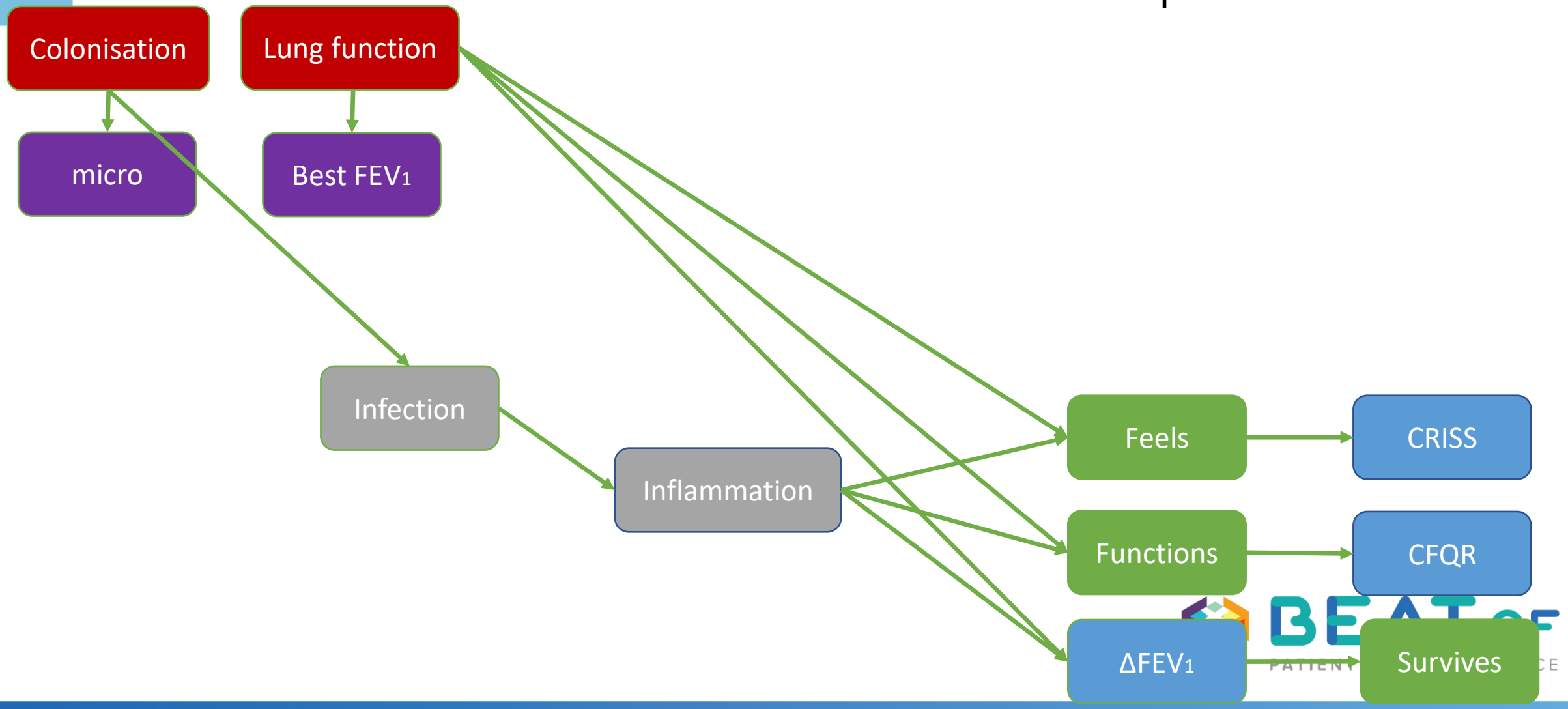

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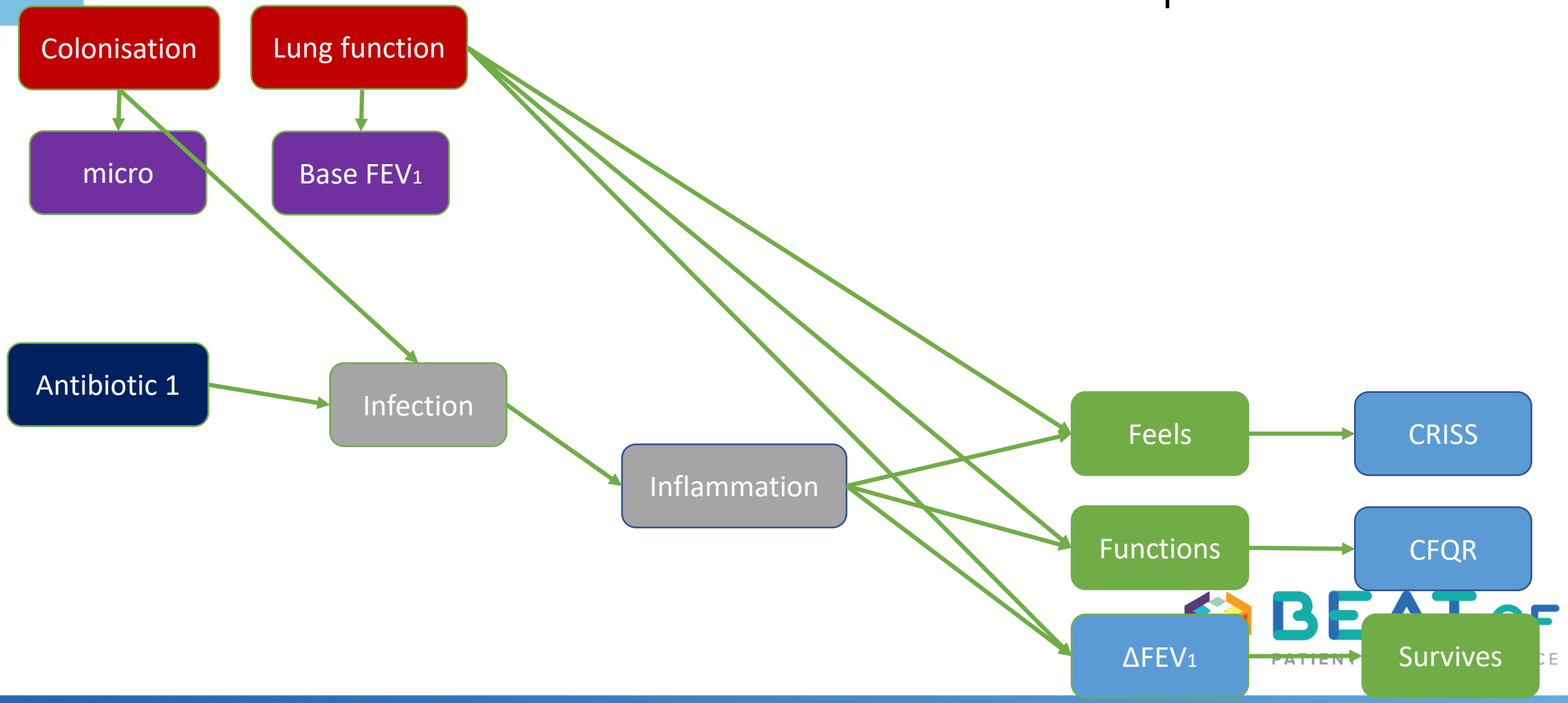

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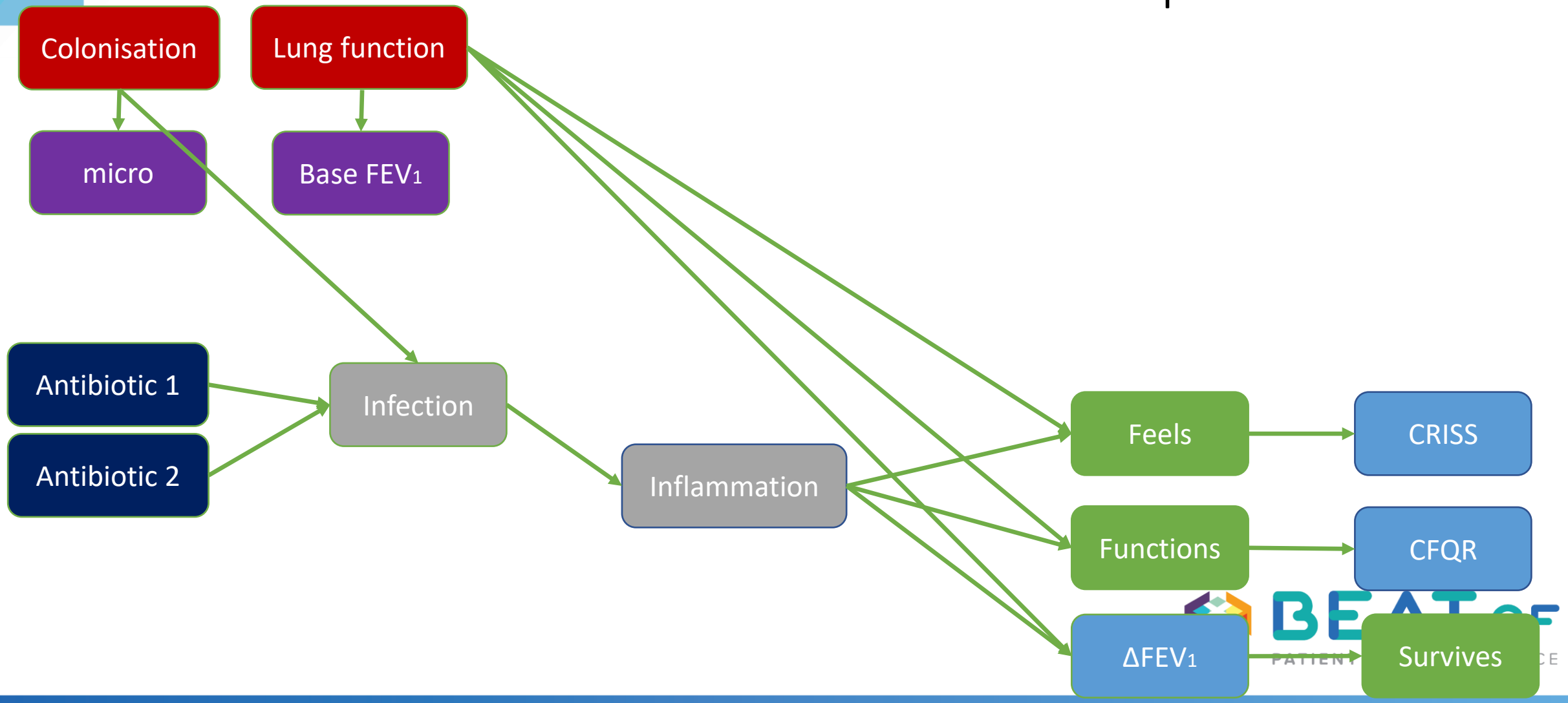

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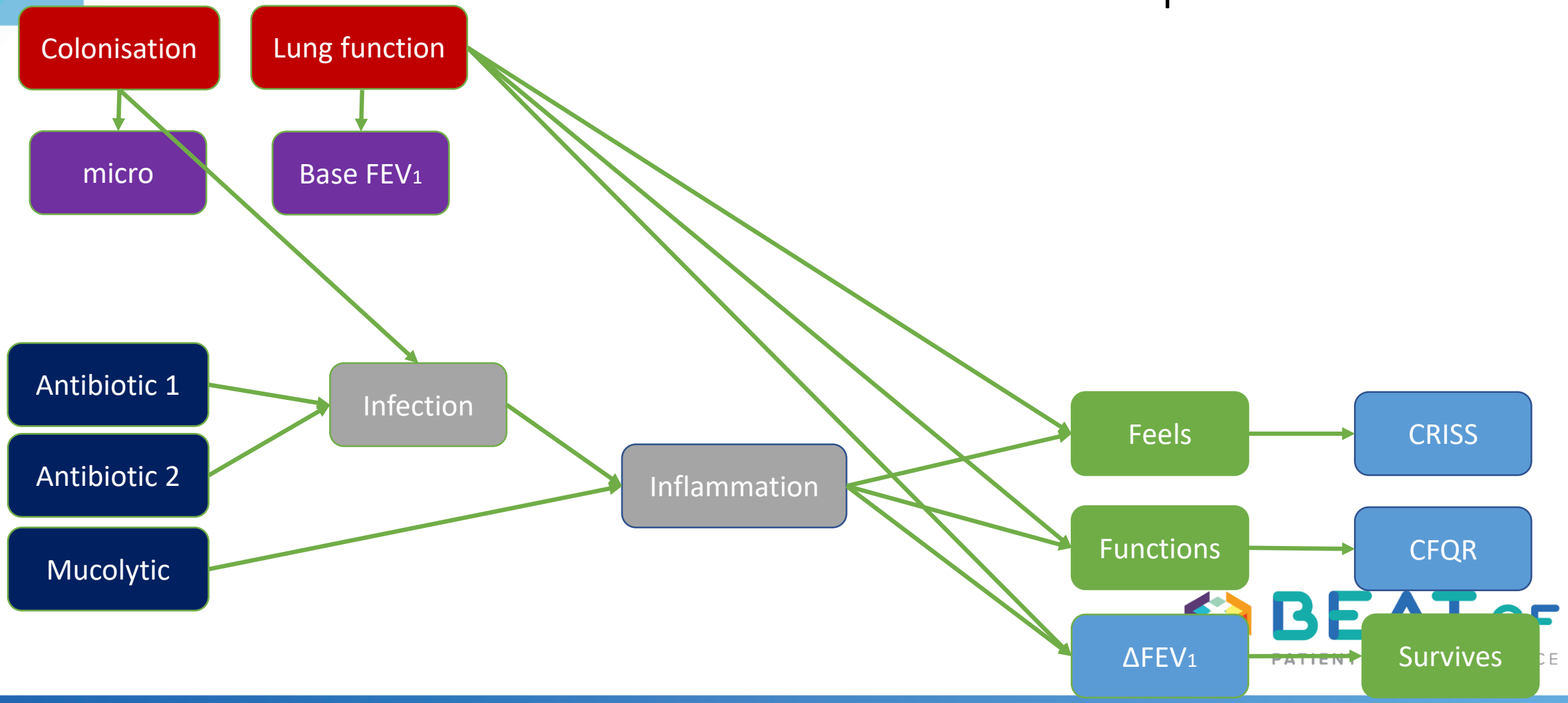

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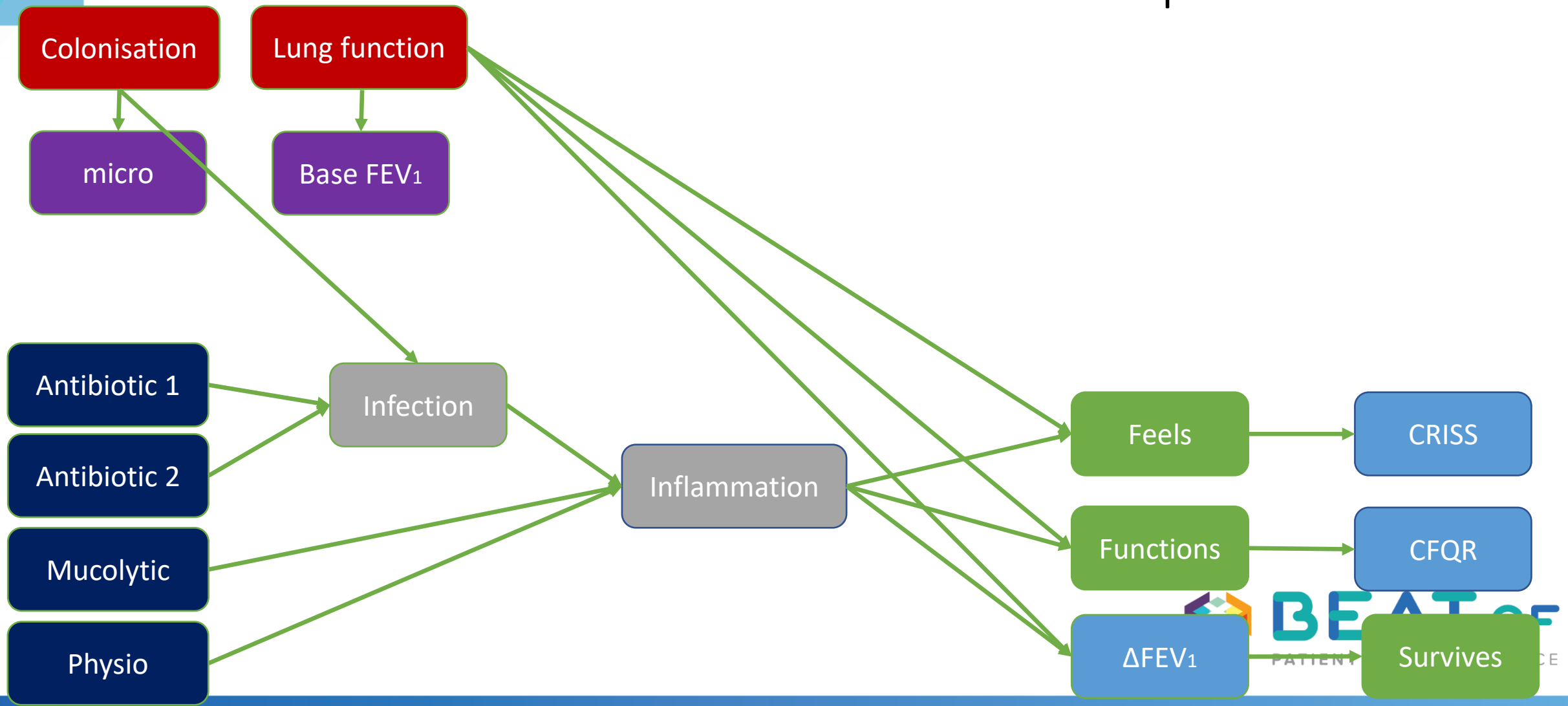

Clinical problem/ question → Causal model

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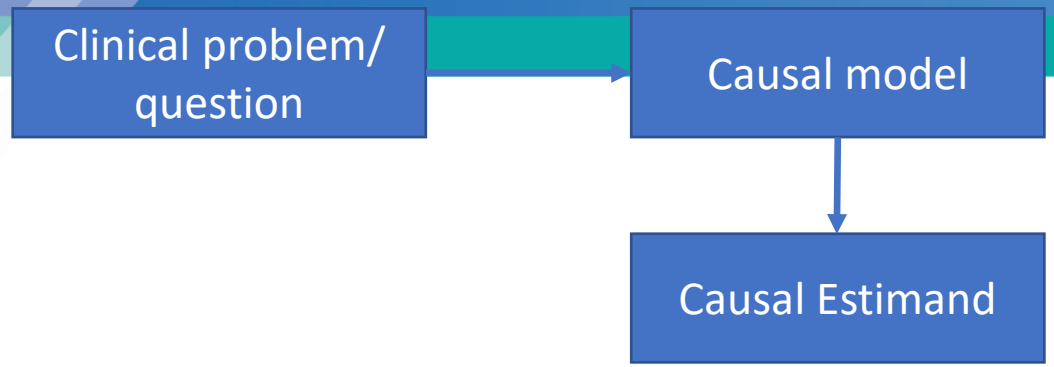

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3. Define the Estimand: PICO + EP

ICH GCP E9 (R1):

Estimand = target of estimation (what) → statistical **estimator** (how)

P: Population(target)

I: Intervention

C: Comparator

O: Outcome/ Endpoint

E: Effect measure (eg risk ratio, average difference)

P: Post-assignment events (death, missing data, loss to follow-up, non-adherence, treatment cross-over)

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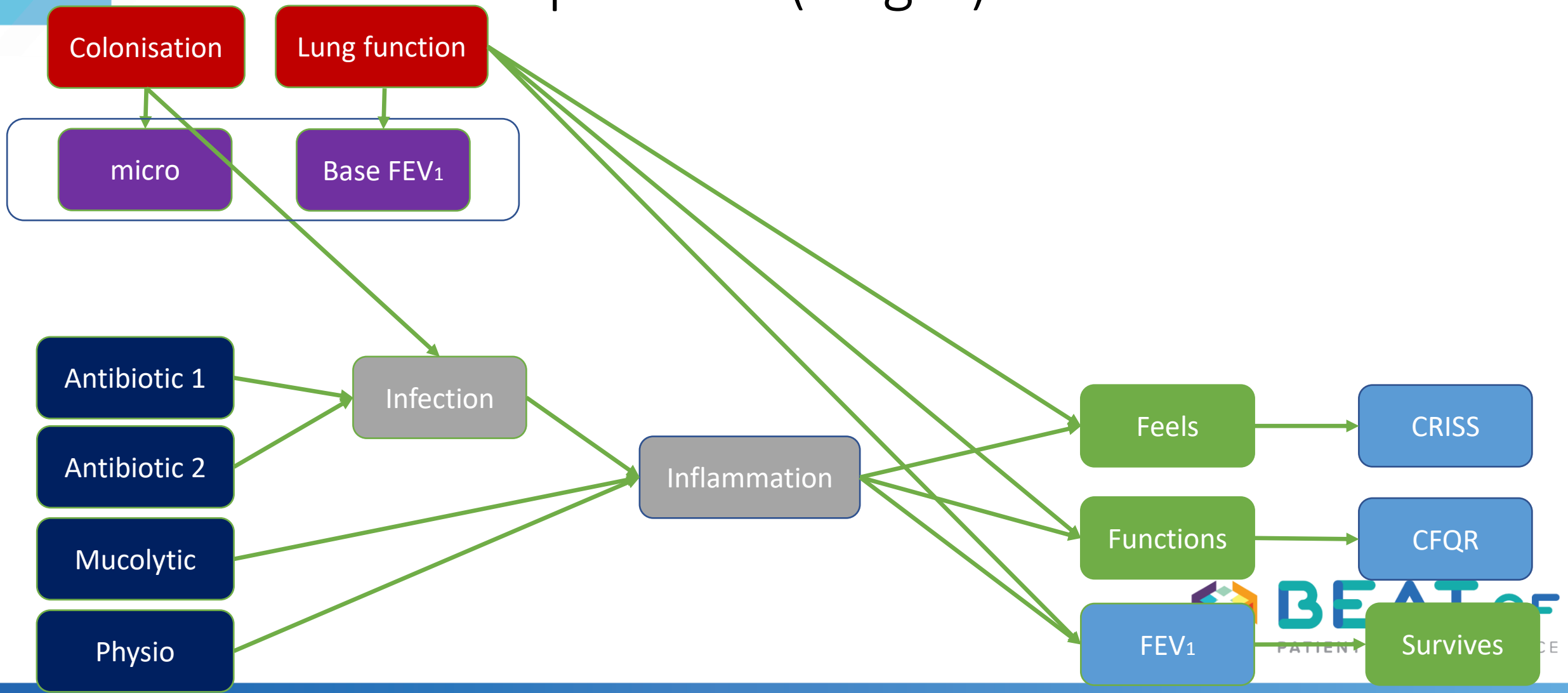
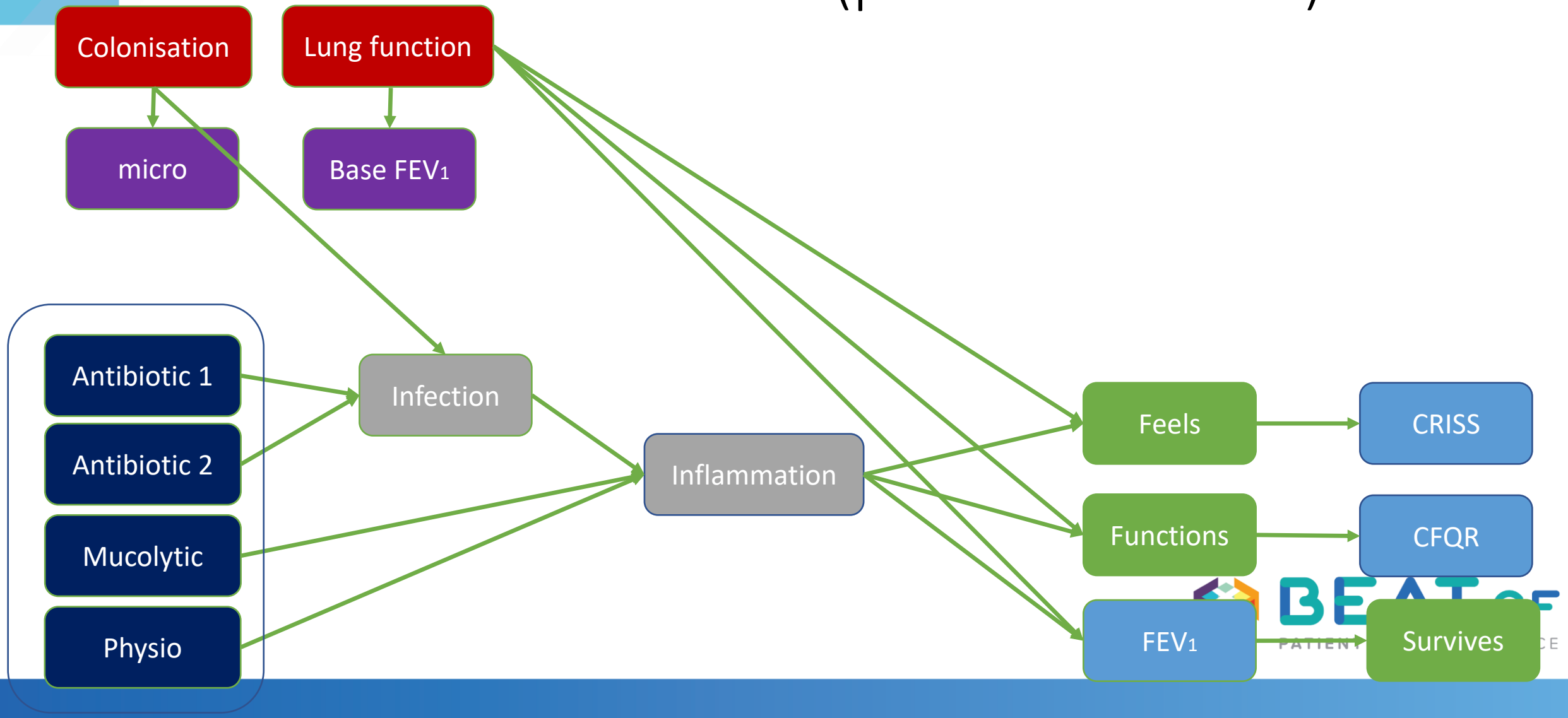
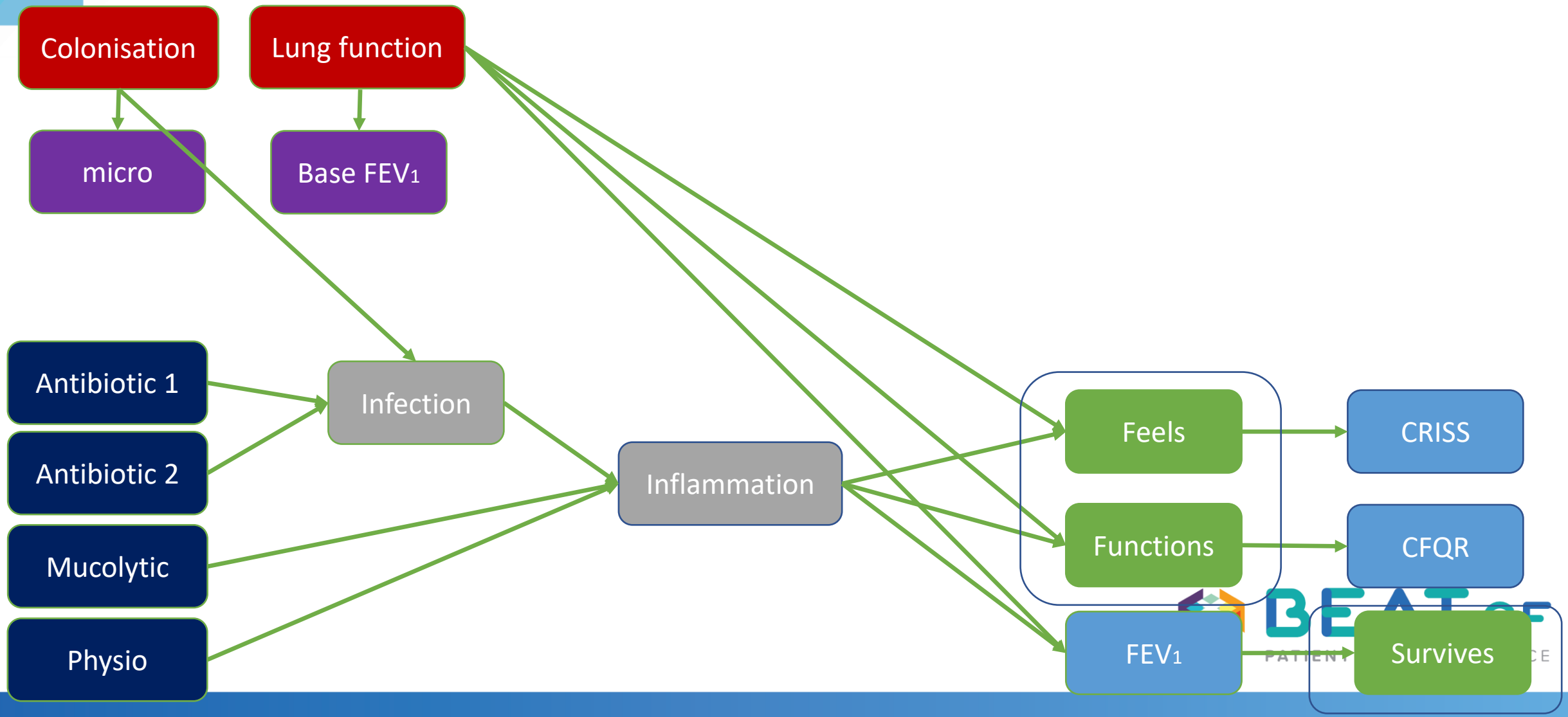
3. Estimand: Population (target)



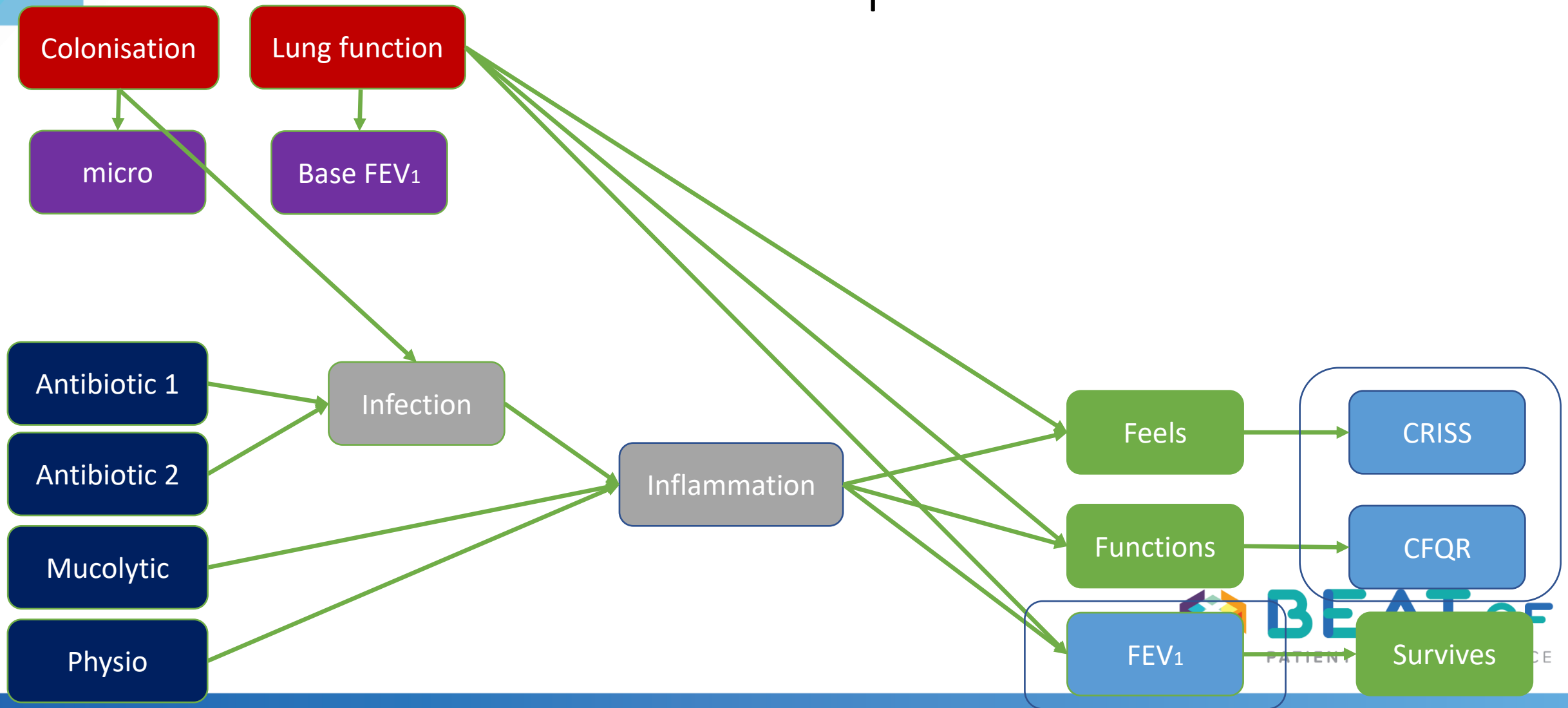
3. Estimand: Intervention (prescribe vs take)



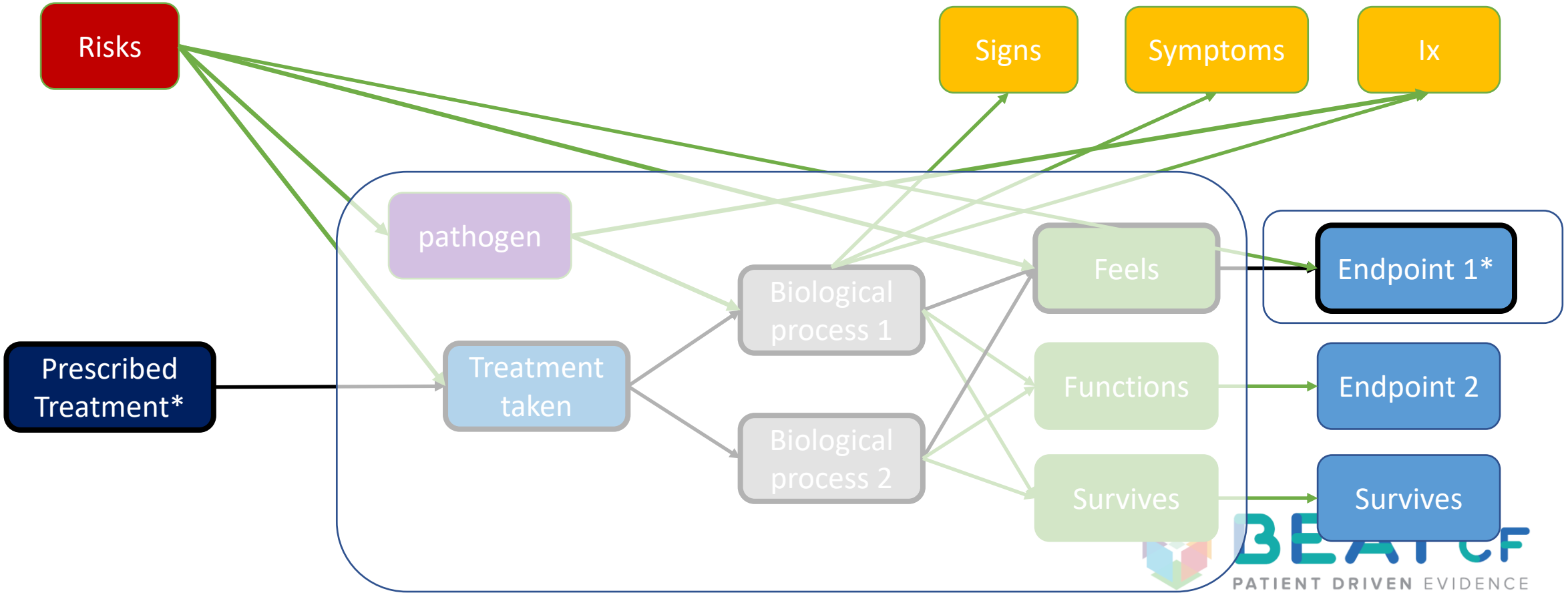
3. Define the estimand: Outcome



3. Define the estimand: Endpoints



3. Define the estimand: **intent-to-treat effect**



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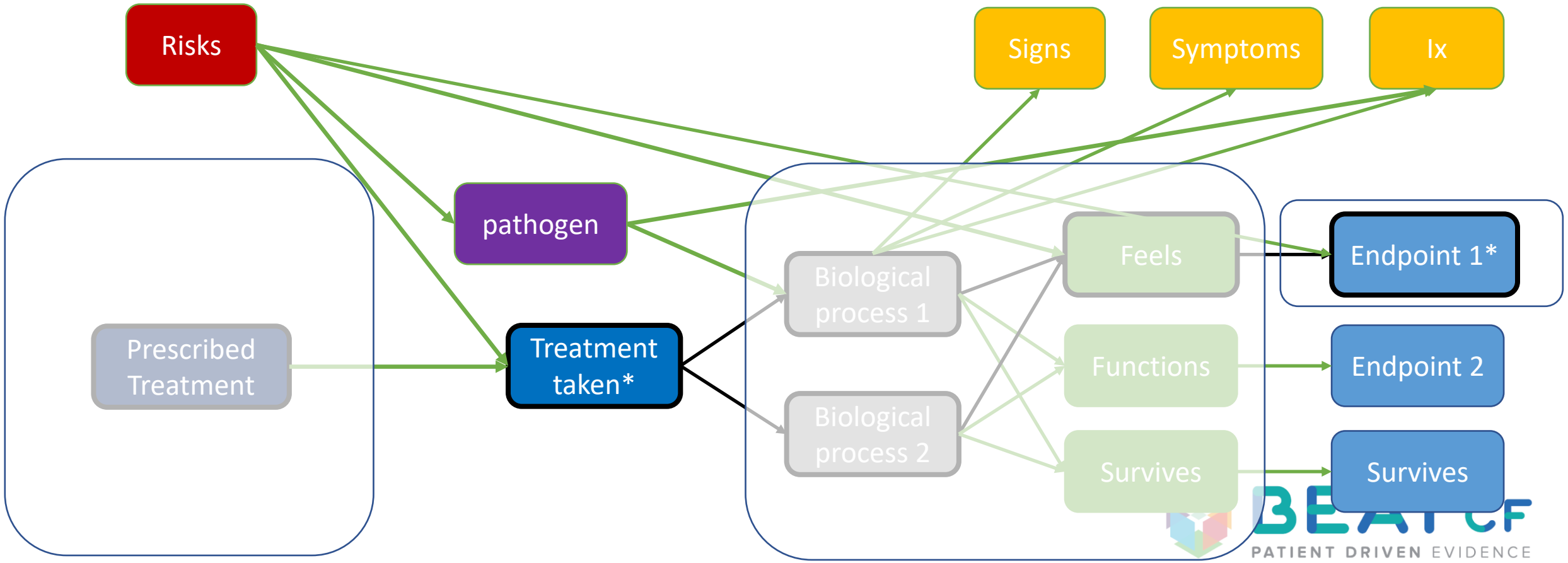
3. Define the estimand: **per-protocol effect**



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Key messages

- Managing CF is complicated (and probably complex)
  - Our trials need to be as simple as possible, but no simpler
- Trials should test alternative *actions*, not *hypotheses*.
- To know how we *should* act, we need to anticipate their potential consequences.
- To do this we *must* have a causal model of the clinical problem
- Causal models, motivated by clinical decision problems, can help us clarify our estimands and design more useful trials.

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