Concepts and Case Study Template for Surrogate Endpoints Workshop

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Medical Product Development

- **GOAL** is to improve how an individual
  - feels
  - functions
  - survives

  } Reflected in a **clinical outcome***

- **CHALLENGES** might include that studies
  - take too long
  - cost too much
  - too risky
  - not feasible

*BEST (Biomarkers, EndpointS, and other Tools) glossary: https://www.ncbi.nlm.nih.gov/books/NBK338448/

Use of Biomarkers in Medical Product Development

- Biomarkers have potential to make medical product development faster, more efficient, safer, and more feasible
- **Biomarker qualification*** is a conclusion, based on a formal regulatory process, that within the stated context of use, a medical product development tool can be relied upon to have a specific interpretation and application in medical product development and regulatory review

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Surrogate Endpoint*

An endpoint that is used in clinical trials as a **substitute** for a direct measure of how a patient feels, functions, or survives.

A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is **expected to predict that clinical benefit or harm** based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

DESIRABLE SURROGATE ENDPOINTS typically satisfy one or more of the following: measured sooner, more easily, less invasively, or less expensively

Most surrogate endpoints are biomarkers or are composite endpoints involving biomarkers.

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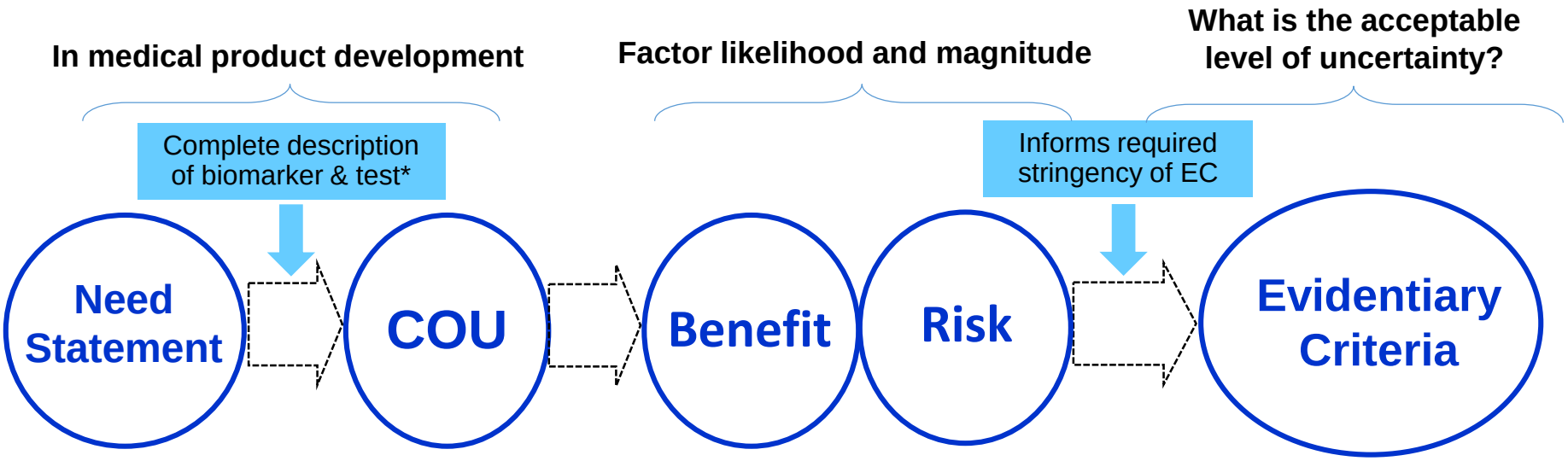
Evidentiary Criteria Framework (updated)



Case study teams have been asked to present information for a **candidate surrogate endpoint** in the format of the general evidentiary criteria framework.

Leptak, Menetski, Wagner, et al. *Sci Transl Med*. 9(417), 2017

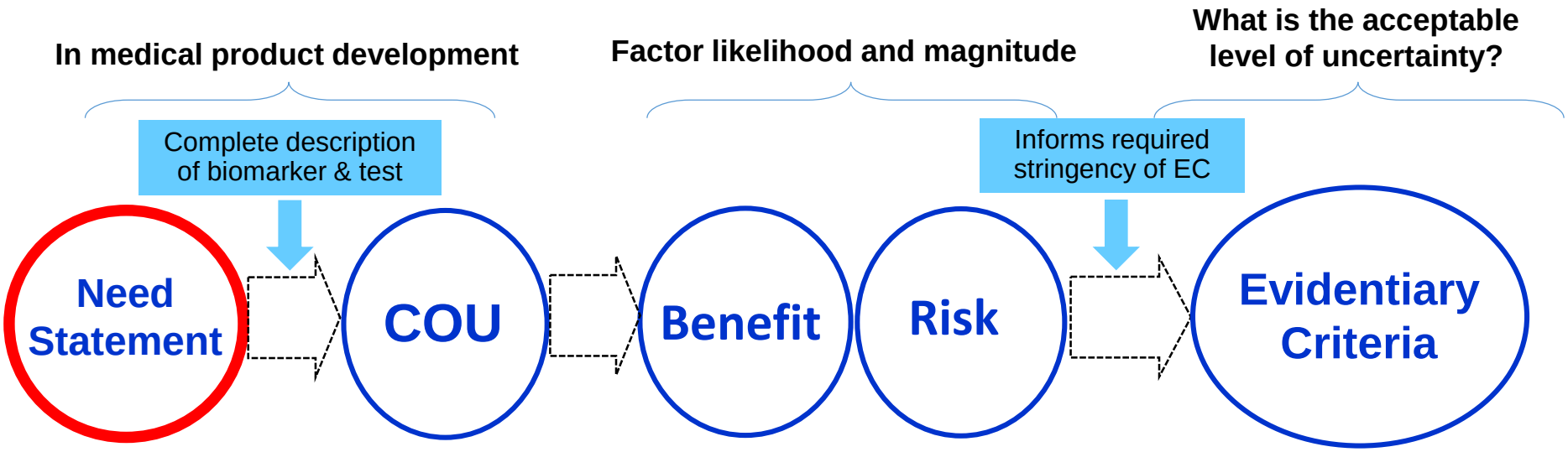
*Analytically validated assay, including required pre-analytic factors

Observations regarding surrogate endpoint discussions

- Much confusion about surrogate endpoint definition and requirements
- Surrogate endpoints must satisfy criteria that overlap with other biomarker classes (roles), e.g.,
  - Surrogate for clinical endpoint $\Rightarrow$ prognostic
  - Prognostic does NOT guarantee surrogacy
- Lots of data doesn't always mean better understanding
  - Some data more useful than others
  - Tradeoffs between depth of biologic/mechanistic understanding and "amount" of data (big n or big p*)

*p = # of measured variables

Evidentiary Criteria Framework (updated)



- *Medical product development need?*
- *Knowledge gap?*

Example situations where surrogates are particularly needed:

- Observation of clinical outcome requires a very long duration study (e.g. 10-20 years)
- True disease outcome not feasible to measure directly (e.g., brain biopsies; only feasible post-mortem)
- Many factors may influence clinical outcome in addition to the particular disease/therapy under study (i.e., noisy outcome variable, salvage therapies)
- Clinical outcome assessment is very subjective and requires very long period of observation (e.g., cognitive function)

Evidentiary Criteria Framework (updated)

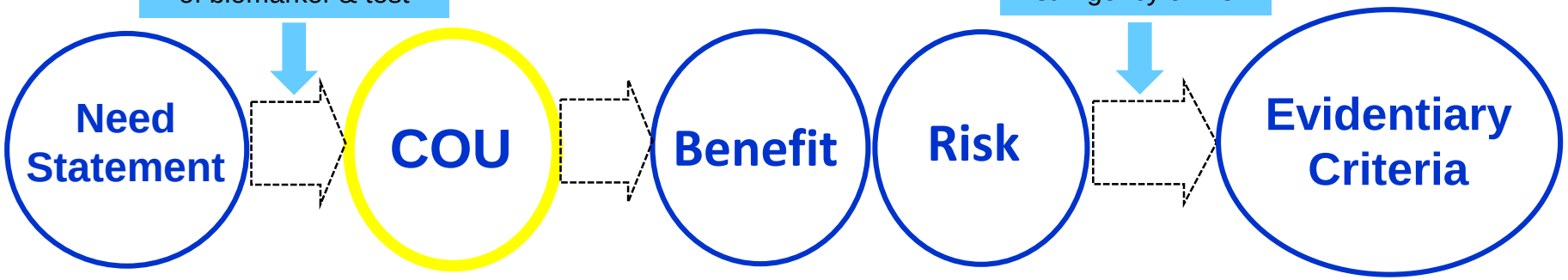
In medical product development

Factor likelihood and magnitude

What is the acceptable level of uncertainty?

Complete description of biomarker & test

Informs required stringency of EC



- *Medical product development need?*
- *Knowledge gap?*

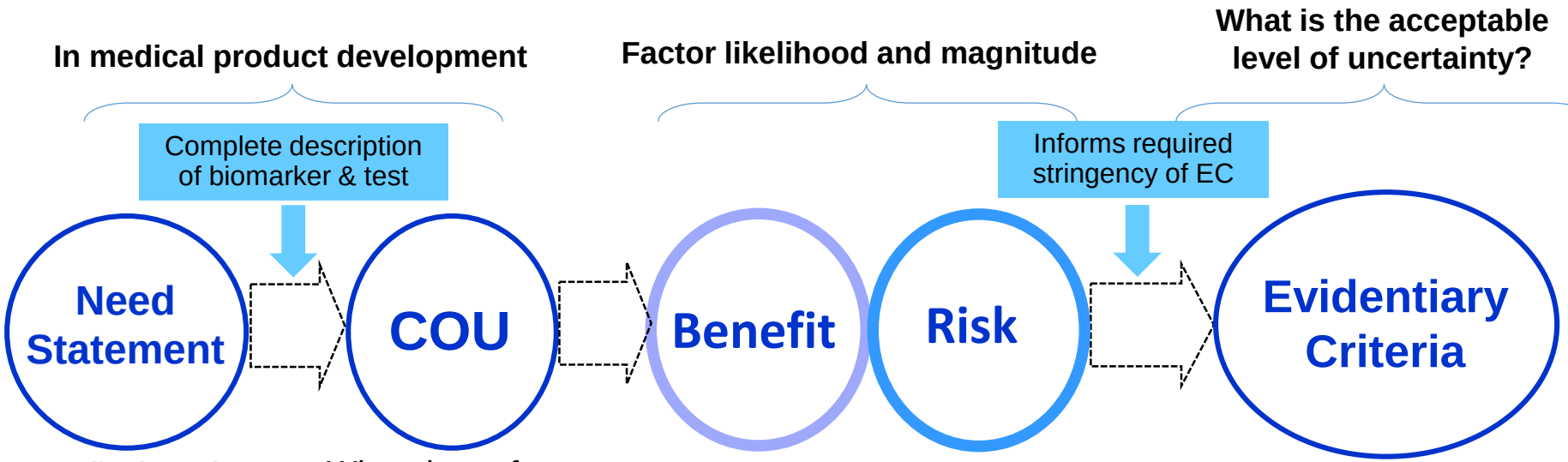
- *What class of biomarker is proposed and what information content would it provide?*
- *What question is the biomarker intended to address?*

Example COUs for surrogate endpoints:

- Seeking a surrogate endpoint to substitute for death from cardiovascular event in clinical trials of lipid lowering agents in patients with prior heart attack
- Seeking a surrogate endpoint to substitute for disease free survival in clinical trials of targeted anti-cancer agents for first line therapy for early stage operable breast cancer

(For each COU, the candidate surrogate endpoint is a biomarker along with a test to measure it.)

Evidentiary Criteria Framework (updated)



- *Medical product development need?*
- *Knowledge gap?*

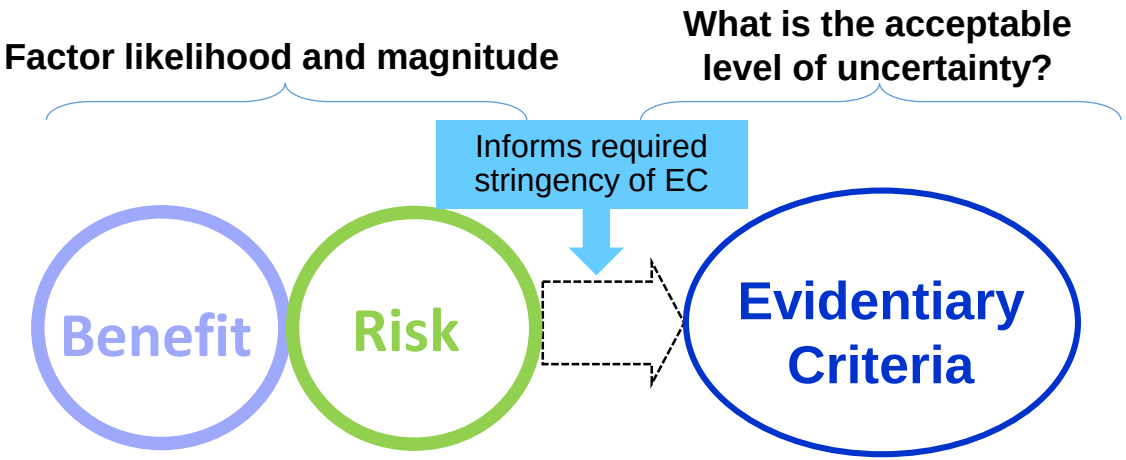
- *What class of biomarker is proposed and what information content would it provide?*
- *What question is the biomarker intended to address?*

- *Potential benefits & risks **to society** and **to individuals**, compared to status quo?*
- *What benefit-to-risk balance is acceptable ?*

Update to original framework

Next slide for elaboration

Evidentiary Criteria Framework (updated)

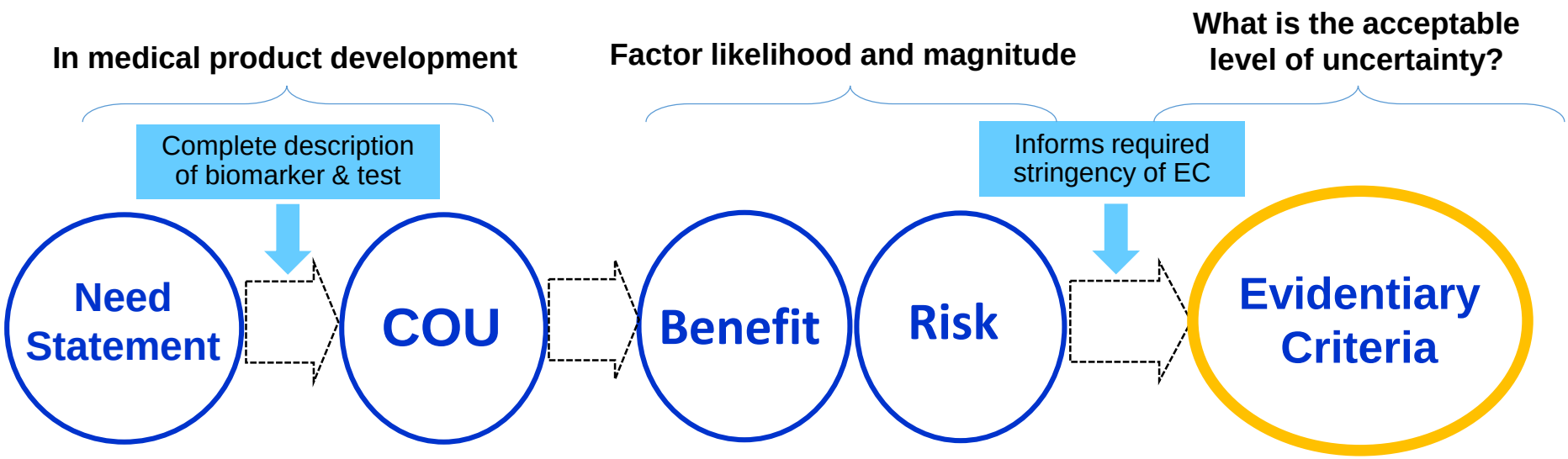


- *Potential benefits & risks to society and to individuals, compared to status quo?*
- *What benefit-to-risk balance is acceptable ?*

Example considerations for surrogate endpoints

	BENEFITS	RISKS
To Society	• Improved sensitivity for drug effect • Improved selectivity (specificity) for drug effect • Earlier treatment access	• Rejecting beneficial drug & population consequences of its non-availability • Accepting ineffective or harmful drug & population consequences of its use
To Individual	• Treatment for disease without options • Earlier removal of non-beneficial treatment	• Treat with drug that does not work or might be harmful • Can't get access to beneficial drug

Evidentiary Criteria Framework (updated)



General evidentiary criteria

- Relationship Between the Biomarker and Clinical Outcome
- Biological
- Type of Data and Study Design
- Independent Data Sets for Qualification
- Assay performance
- Statistical Methods to Use

Evidentiary criteria of importance for surrogate endpoints

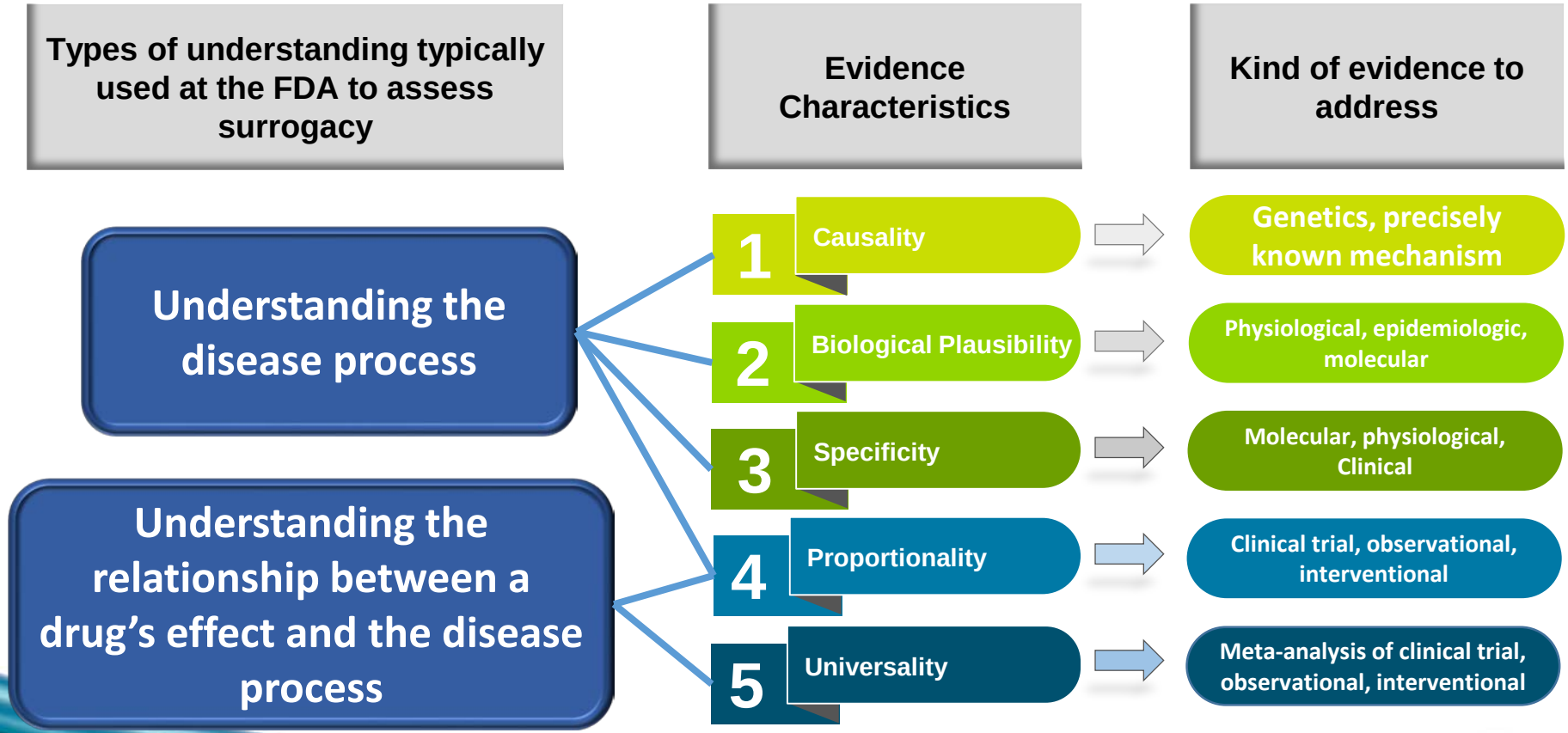
- Biological plausibility
- Causality
- Universality
- Proportionality
- Specificity

Update to original framework

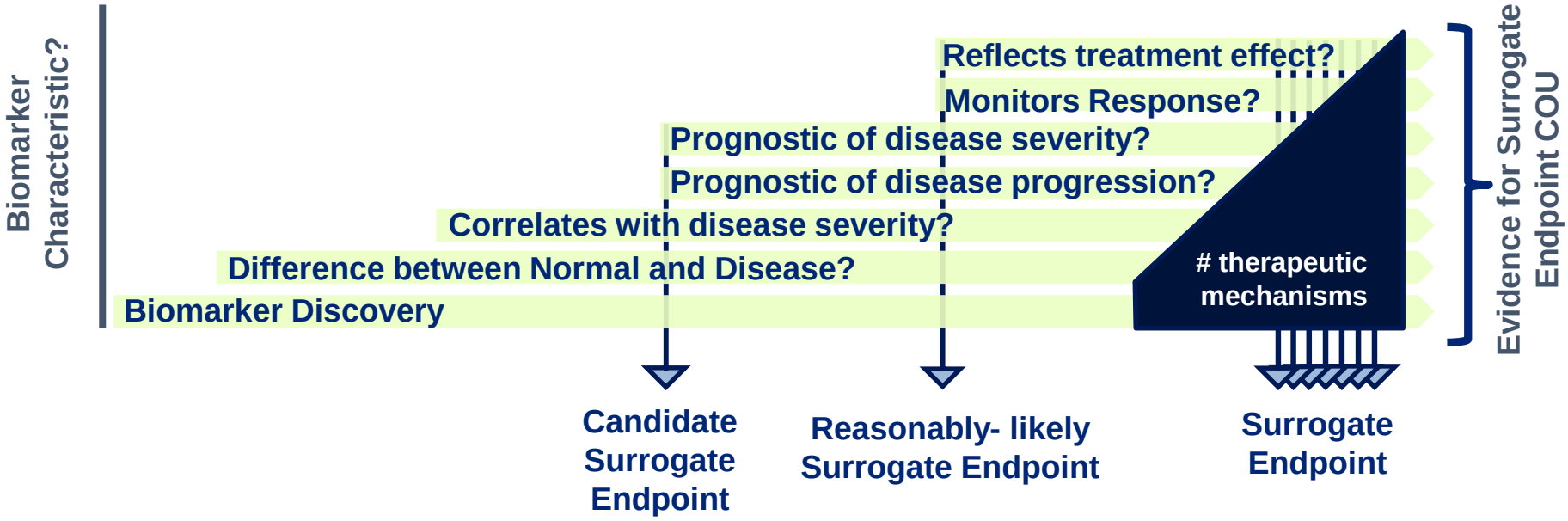
Issues of focus related to surrogate endpoint (biomarker) evidence

- **Causality**
  - Is there a compelling case for surrogate being on the single direct causal pathway to disease outcome, so less need for evidence of universality?
- **Plausibility**
  - Is the biology of the surrogate so compelling that it adds to the weight of empirical evidence for acceptance?
- **Specificity and potential for complicating effects**
  - Other factors affecting disease outcome, including off target effects of drugs
- **Proportionality**
  - To what extent does the magnitude of change in the surrogate explain the disease or the magnitude of change in disease status or burden?
- **Universality**
  - To what extent is there evidence across drug mechanisms or across different populations?

Link to previous FDA vocabulary and workshop terms



Surrogate Endpoint Evidentiary Progression



Surrogate Endpoint

From a U.S. regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be characterized by the level of clinical evidence:

- **Validated**
  - An endpoint supported by a **clear mechanistic rationale and clinical data** providing strong evidence that an effect on the surrogate endpoint predicts a clinical benefit. Therefore, it can be used to **support traditional approval** without the need for additional efficacy information
- **Reasonable likely**
  - An endpoint supported by **clear mechanistic and/or epidemiologic rationale but insufficient clinical data** to show that it is a validated surrogate endpoint. Such endpoints can be used for **accelerated approval for drugs or expedited access for medical devices**. In the case of accelerated approval for drugs, **additional trial data**, assessing the effect of the intervention on the clinical benefit endpoint of interest will be collected in the **post-marketing** setting to verify whether an effect on the reasonably likely surrogate actually predicts clinical benefit in the specific context under study

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Prognostic is not sufficient for surrogacy

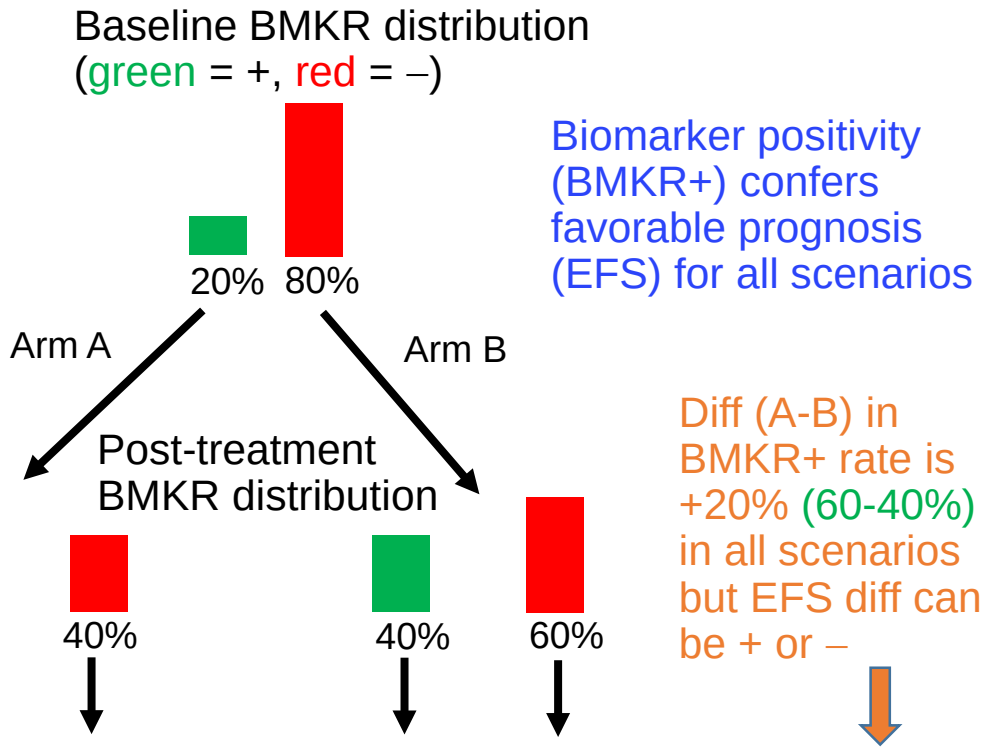
Prentice criteria ("ideal")

- Surrogate must correlate with "true" clinical outcome
- Treatment effect on the surrogate should capture full effect of treatment on "true" clinical outcome

Pragmatic criteria

- Magnitude of treatment effect on the surrogate reliably predicts magnitude of effect on "true" clinical outcome (clinical benefit*)

*Assume long term event-free survival (EFS) is the outcome used to assess clinical benefit



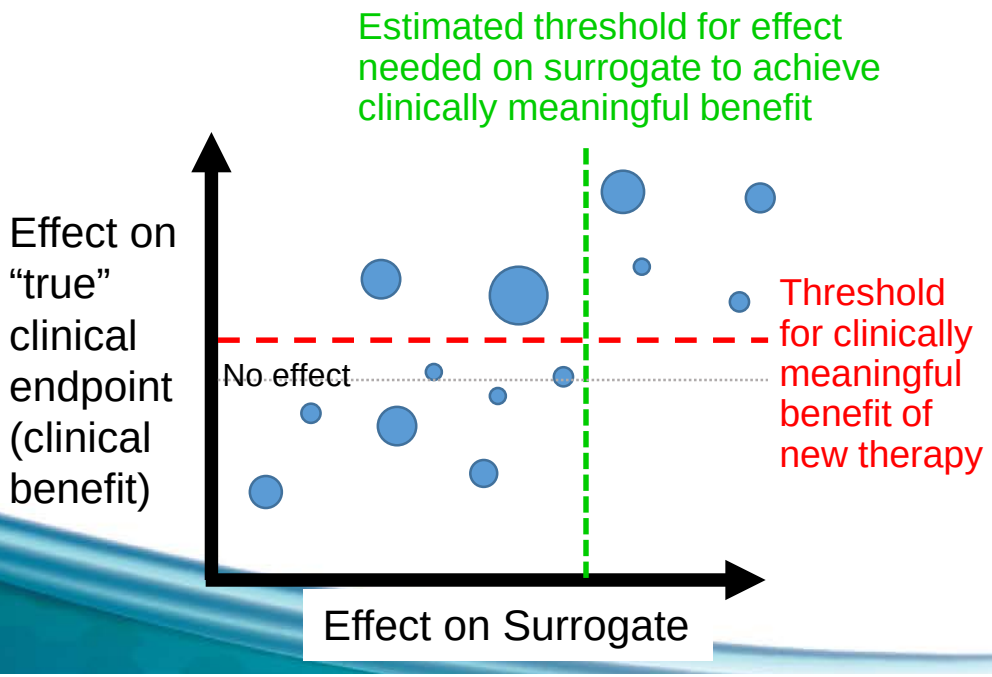
Biomarker positivity (BMKR+) confers favorable prognosis (EFS) for all scenarios

Diff (A-B) in BMKR+ rate is +20% (60-40%) in all scenarios but EFS diff can be + or –

Scenario	Arm A, EFS for BMRK+	Arm A, EFS for BMKR–	Arm A, Overall EFS	Arm B, EFS for BMKR+	Arm B, EFS for BMRK–	Arm B, Overall EFS	EFS Diff (A-B)
1 (Prentice)	80%	20%	56%	80%	20%	44%	12%
2	90%	20%	62%	60%	40%	48%	14%
3	60%	20%	44%	70%	30%	46%	–2%
4	80%	5%	50%	90%	40%	60%	–10%

Meta-analytic methods

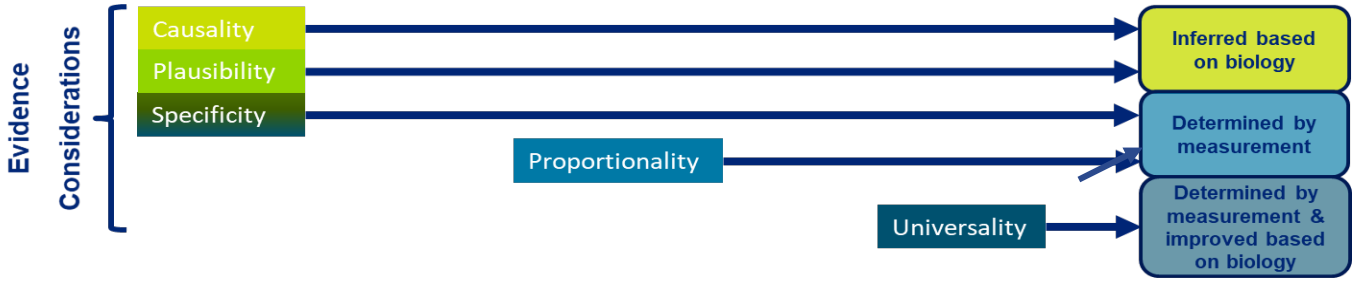
- Directly analyze how reliably a trial-level effect on a candidate surrogate endpoint predicts trial level effect on “true” clinical endpoint (clinical benefit)
  - Patient-level data permits assessment of both individual-level (prognostic) and trial-level “surrogacy”
  - Trials must be representative of COU population (preferably comprehensive)



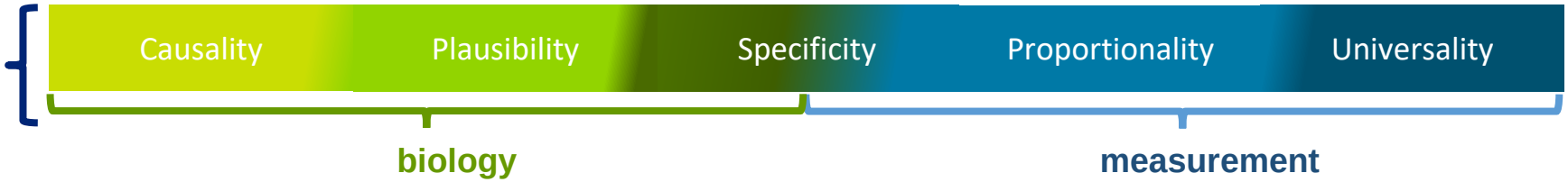
- Causality: randomized controlled trials
- Biological plausibility: disease biology and drug mechanism
- Specificity: degree of scatter from line (trial-level effects combine direct and indirect effects of treatment)
- Proportionality: slope of scatterplot
- Universality: depends on selection of trials for the meta-analysis (considering patient population and drug mechanistic class)

Each circle represents a clinical trial; size indicates amount of information (e.g., # of events)

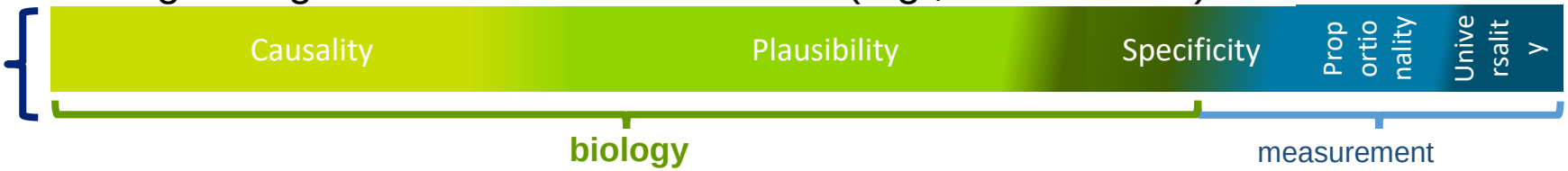
Evidentiary Balance



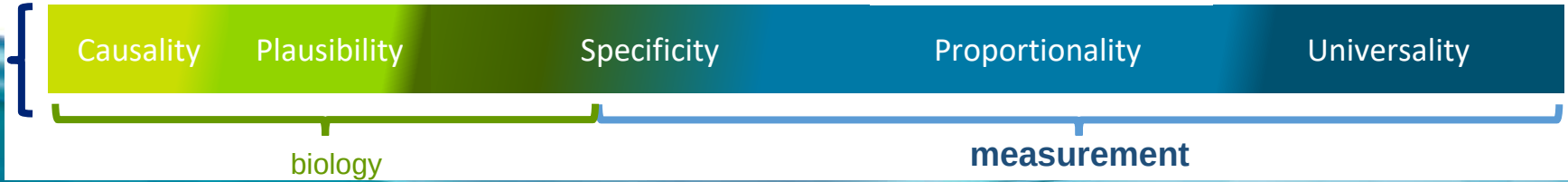
Balanced Evidence Considerations (example, LDL)



Strong Biologic Evidence Considerations (e.g., rare disease)



Strong Experimental Evidence Considerations (e.g., meta-analyses, big data)



Evidence Considerations

Surrogate Endpoint Case Studies

The approach represented by the framework will be tested against six specific case studies of surrogate endpoints in drug development. As a group these cases span the spectrum of uncertainty of the surrogates' demonstrated ability to predict clinical benefit, and therefore will be helpful in assessing the framework's elements:

Case Study	Characteristics of challenge
LDL in cardiovascular disease	Accepted Surrogate
HDL in cardiovascular disease	Insufficient evidence
A multicomponent machine learning approach for cardiovascular disease	Multiplex approach very early in the development process, likely more common in the future
Minimal residual disease in Multiple Myeloma	Candidate surrogate endpoint with developed data package and understanding, high need, early in the qualification process
Polycystic Kidney Disease, a prognostic marker moving to surrogate endpoint	Candidate surrogate endpoint. Good example of potential transition of prognostic biomarker to surrogate
Alexander's Disease, a rare disease of a single gene mutation in GFAP	Candidate surrogate endpoint in rare disease; representative of strong understanding of disease pathogenesis