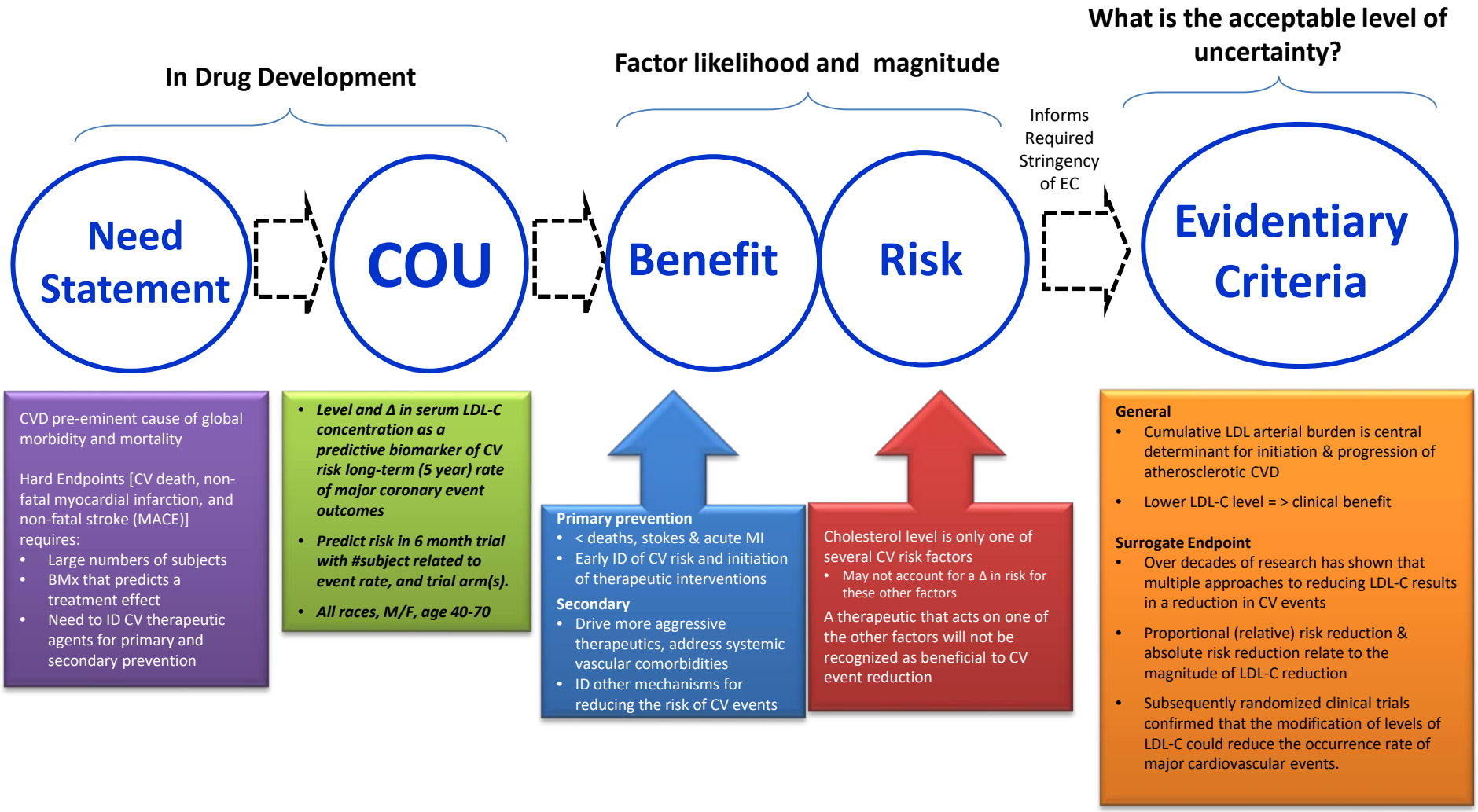
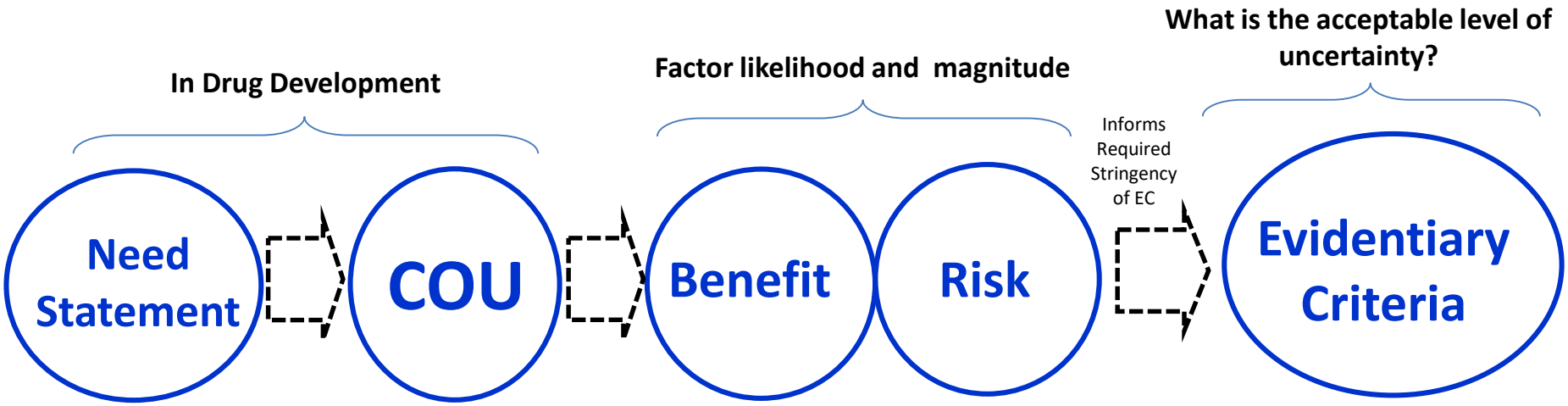
LDL: Biomarker Evidentiary Framework



HDL: Biomarker Evidentiary Framework



CVD pre-eminent cause of global morbidity and mortality

Can we reduce risk BEYOND what statins have achieved for LDL-C?

Optimal agents with BOTH lower LDL-C and RAISE HDL

- ***Level and Δ in serum HDL concentration as a predictive biomarker of CV risk long-term (10 year) rate of major coronary event outcomes***
- ***Predict risk in 6 month trial with 1000 subjects - related to event rate, and trial arm(s).***
- ***All races, M/F, age 40-70***

Primary prevention
- < deaths, stokes & acute MI
- Early ID of CV risk and initiation of therapeutic interventions

Secondary
- Drive more aggressive therapeutics, address systemic vascular comorbidities
- ID other mechanisms for reducing the risk of CV events

Cholesterol level is only one of several CV risk factors
- May not account for a Δ in risk for these other factors

A therapeutic that acts on one of the other factors will not be recognized as beneficial to CV event reduction

General
- Multiple LDL-C lowering drugs raise HDL levels
- CEPT deficient patient Subjects Have Increased HDL and Apo A1 Levels

Surrogate Endpoint
- Research has shown that elevating HDL opposes atherothrombosis
- The modification of HDL-C levels by CETP inhibition, in and of itself, does not appear to provide clinical benefit
- Subsequently randomized clinical trials confirmed that the modification of levels of HDL do not provide universal reduction in the occurrence rate of major cardiovascular events

Basically the same as LDL-C (or for other CVD factors)

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BIOMARKERS CONSORTIUM

FNIH

Machine Learning CVD: Biomarker Evidentiary Framework

Statement of need
- Despite some recent advances, most cardiovascular risk remains unresolved by today's treatments
- Cardiovascular outcomes trials are prohibitively expensive (20,000 subjects and 3-5 years is typical) because of the low incidence of events.

Benefits of the marker
- Earlier benefits = lives saved on drug
- Reduced costs, more drugs tested
- Lives saved during outcomes trial
- Reduced costs of drug development, earlier access to benefits

Risks of the marker
- Ineffective drug is approved
- Lost benefits of drug & increased costs
- Safety issue discovered during marketing = lives lost

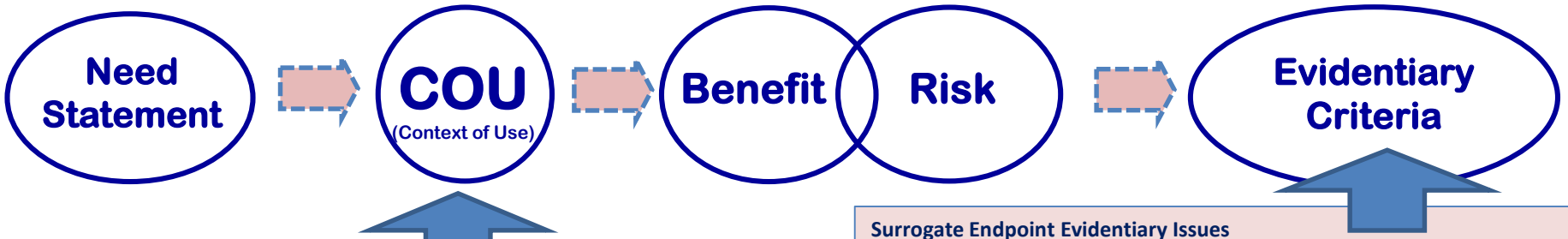
What is the acceptable level of uncertainty?
- *The patient population is averse to additional risk.*

In Drug Development

Factor likelihood and magnitude

Informs Required Stringency of EC

What is the acceptable level of uncertainty?



1. As a surrogate endpoint in pivotal clinical trials of cardiovascular drugs
2. As a surrogate endpoint for cardiovascular safety in pivotal trials of non-cardiovascular drugs

Surrogate Endpoint Evidentiary Issues
- Universality
  - assessed across a wide range of geographies and ethnicities
  - the sensitivity to change from beneficial, neutral and adverse effects must be demonstrated comprehensively
- Plausibility: A plausibility story can be constructed post-hoc from protein functions and pathways but this is not available *a priori*.
- Causality: No claims of causality will be made
- Proportionality: equal to or superior to existing risk factor models
- Specificity and potential for off target effects: Disease specificity is demanded of the pattern

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CONSORTIUM

MRD-MM: Biomarker Evidentiary Framework

- Clinical outcomes take many years to develop
  - Longer, more expensive clinical trials will delay availability of active clinical agents to patients
  - Less industry interest in developing new myeloma drugs
- Urgent need for clinical monitoring of MRD in MM to track patient cancer progression and treatment response

Benefits of the marker

- The patients would benefit because it would allow more rapid development of therapies and more accurate tracking of treatment response. ***Increased likelihood to be used.***
- The field would be able to seek regulatory approval faster for drugs and biomarkers.
- This biomarker will allow quantitative testing in a population.

Risks of the marker (*magnitude of potential risks with MRD is low*)

- Novel therapeutic approved that doesn't impact traditional clinical benefit measures, OS.
- Early trial termination due to incorrect futility analysis if benefit not seen with MRD assessment
- Patients may not receive treatment that improve survival
- Achieving MRD negativity may not correlate with OS (Additional treatment may not be necessary in certain patients)

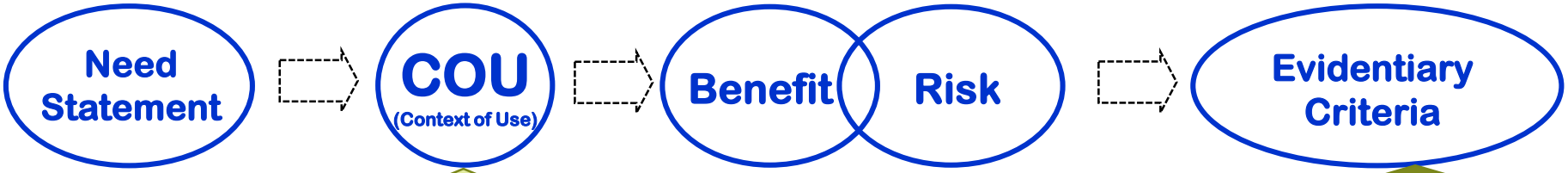
What is the acceptable level of uncertainty?

- ***The patient population is motivated to take on more risk to help achieve beneficial therapies.***

In Drug Development

Factor likelihood and magnitude

Informs Required Stringency of EC



MRD, as assessed via bone marrow aspirate, measured using a validated assay, is a response biomarker that can be used in patients with multiple myeloma to assess response to treatment correlated with outcome

Surrogate Endpoint Evidentiary Categories

- Biological plausibility
  - Multiple testing methods
  - Good correlation with disease
- Causality
  - Residual disease cells are what is being tested *(reasonably likely, but hard to prove)*
- Universality
  - Good initial clinical data, additional clinical data needed for meta-analyses for specific COUs
- Proportionality
  - Specific meta-analysis needed to prove this
- Specificity
  - Residual disease cells are what is being tested *(reasonably likely, but hard to prove)*

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TKV: Biomarker Evidentiary Framework

Statement of need

- TKV has been evaluated by the FDA and approved as a clinical trials enrichment biomarker for clinical trials in ADPKD
- Although progress has been made toward approval of htTKV as a surrogate endpoint or response biomarker, this is not yet complete
- **Significant need is present to allow for testing of more therapies in the most common hereditary renal disease accounting for 10% of ESRD patients under 65 years of age.**

Benefits of the marker

- Earlier benefits = lives saved on drug, shorter trial duration
- Increased safety with only those at risk for progression tested
- Time saved without the need for dialysis or transplant
- Reduced costs of drug development, earlier access to benefits

Risks of the marker

- A drug that benefits cyst burden and does not slow progression to ESRD
- Lost benefits of drug & increased costs
- Safety issue discovered during marketing = lives lost

What is the acceptable level of uncertainty?

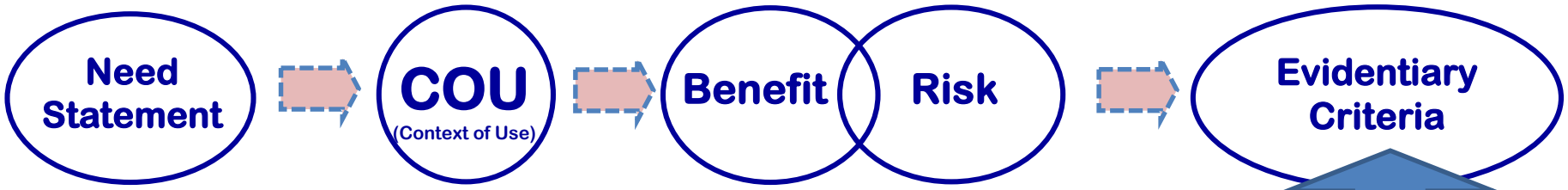
- *The patient population is highly functional and would not tolerate high longer term side effects.*

In Drug Development

Factor likelihood and magnitude

Informs Required Stringency of EC

What is the acceptable level of uncertainty?



1. *A surrogate endpoint for use in clinical trials* of early stage ADPKD where kidney function remains stable despite progressive increase in cyst burden
2. Reduced need for long trials aimed at loss of kidney function that would take decades to complete

Surrogate Endpoint Evidentiary Issues

- Universality
  - htTKV has been used in many countries in multiple testing sites
  - the sensitivity to change from beneficial, neutral and adverse effects can be easily detected. Studies have focused on adults and those with early disease
- Plausibility: Evidence exists today for plausible use of the htTKV marker in disease progression.
- Causality: Impact on cyst burden or htTKV and its consequences on progressive loss of kidney function can be demonstrated
- Proportionality: equal to or superior to existing traditional models involving kidney function
- Specificity and potential for off target effects: The measurement is the disease, ie cyst growth and expansion and cyst burden.

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GFAP: Biomarker Evidentiary Framework

Statement of need
- Clinical features may develop over many years and may be variable
- Clinical outcomes are not specific to AxD (gait and language abnormalities)
- No clinical outcome assessments (COA) validated for AxD
- Lack of COA would prevent adequately testing dosing and response
- Novel ASO based therapies tested in rodent models
- Urgent need for clinical trial readiness

Benefits of the marker
- The patients would benefit because direct brain measurement of GFAP is not accessible. *CSF testing less invasive*
- The current COA relies on manifesting severe signs of disease, generally irreversible and developing over years. *Would allow more rapid development of therapies with real-time assessment of impact of therapies*
- This biomarker will allow *quantitative testing in a population*.

Risks of the marker
- GFAP levels may not be directly related to phenotype. *Preliminary data suggests that GFAP correlates to disease severity. [risk not likely and low magnitude]*

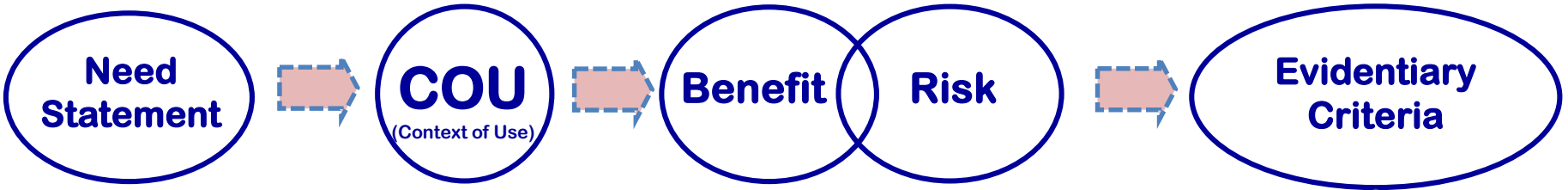
What is the acceptable level of uncertainty?
- *The patient population is motivated to take on more risk to help achieve beneficial therapies.*

In Drug Development

Factor likelihood and magnitude

Informs Required Stringency of EC

What is the acceptable level of uncertainty?



The surrogate endpoint will be used to measure response in individuals with AxD by assessing GFAP in CSF or plasma before and some time after treatment to predict clinical outcomes at a later date

Surrogate Endpoint Evidentiary Issues
- Biological plausibility
  - Genetics
  - Animal model data
- Causality-Genetics
- Universality
- Proportionality-GFAP levels proportional to age of onset
- Specificity-GFAP aggregates are the hallmark of the disease

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