Relatively Likely and Validated Surrogate Endpoints

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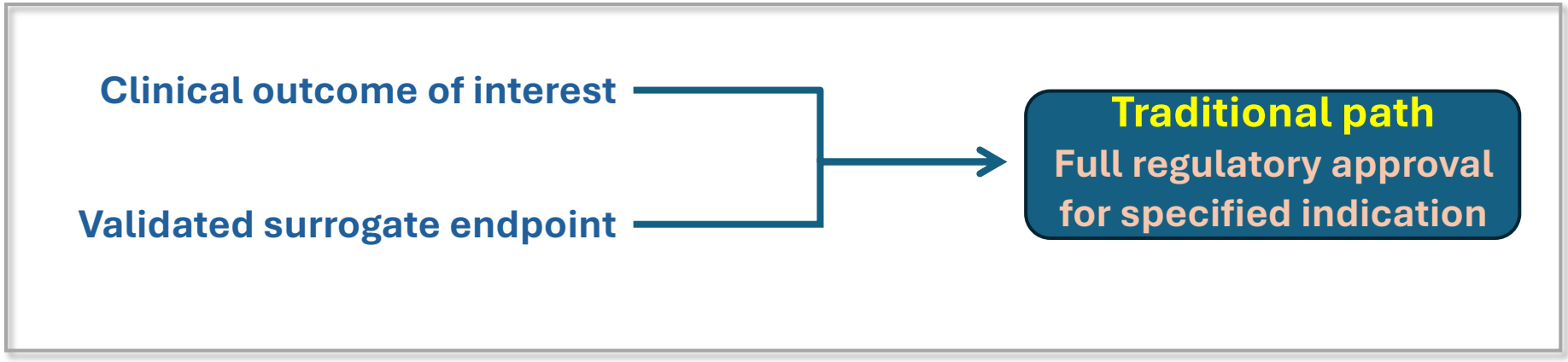
Disclosures

- I am an employee of GSK Pharmaceuticals
- Any opinions expressed are my own and do not necessarily represent those of my employer

Regulatory Drug Approval

- ***Approval for a drug must be based on endpoints that focus on how a patient***
  - ***Feels***
  - ***Functions***
  - ***Survives***



Categories of clinical validation of surrogate endpoints and potential surrogate endpoints

Category	Feature	Type of approval	Need for full approval
Validated surrogate	Known to predict clinical benefits with a clear mechanistic rationale	Traditional	No additional efficacy information is required before or after approval
Reasonably likely surrogate	Reasonably likely to predict a drug's intended clinical benefit	Accelerated	Additional trial data assessing the effect of the intervention on the clinical benefit of endpoint of interest needs to be collected in the postmarketing setting to verify the effect
Intermediate endpoint			
Candidate	Still under evaluation as there is insufficient evidence	N/A	N/A

Adapted: Chen et al. Surrogate Endpoints in Drug Development: A Review of Statistical and Regulatory Perspectives and Applications, Wiley Interdisciplinary Reviews: Computational Statistics, 2025; 17:e70014

Levels of clinical validation of surrogate endpoints and potential surrogate endpoints

Category	Level of clinical validation	Type of measure
Validated surrogate	Have sufficient evidence to show they **reliably predict** a clinical benefit	Typically, a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit.
Reasonably likely surrogate (RLSE)	Have a strong scientific basis, but the full clinical **evidence to confirm** their predictive power is **not yet available**.	
Intermediate endpoint	Same as RSLE	A measure of a therapeutic effect that can be measured earlier than irreversible morbidity or mortality and is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

FDA webpage Accelerated Approval | FDA: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval Content current as of: 02/24/2023

Establishing the validity of a surrogate endpoint

- ***Biologic plausibility****:* Scientifically grounded relationship between the surrogate and the clinical endpoint it is intended to substitute.

- ***Epidemiologic evidence****:* Empirical evidence from observational studies or previous clinical trials should support the relationship. Multiple studies conducted across different populations or settings should consistently demonstrate a strong association between the surrogate and the clinical endpoint

- ***Analytical validation****:* Statistical analyses should be conducted to assess the strength and consistency of the relationship between the surrogate endpoint and the clinical outcome. (e.g., correlation coefficients, regression models, or other statistical methods to quantify the association).

- ***Surrogate threshold effect (aka, meaningfulness)****:* The surrogate endpoint should show a threshold effect, meaning that a specific change in the surrogate is associated with a predictable change in the clinical outcome. This helps establish a meaningful cutoff or target for the surrogate endpoint.

Example: HbA1c is a well established validate surrogate endpoint

	Diabetes Control and Complications Trial (DCCT)	United Kingdom Prospective Diabetes Study (UKPDS)
Patient population	Type 1 Diabetes	Type 2 Diabetes
Study size	1,441 participants	3,867 participants
Follow up duration	Mean 6.5 years	Median 10 years
	• Showed that maintaining blood glucose close to the non-diabetic range reduced the onset and progression of retinopathy (49-63%), nephropathy (54-56%), and neuropathy (60%) in T1D. • Established a target HbA1c of <7% for T1D patients.	Demonstrated that a 1% reduction in HbA1c was associated with a 21% reduction in diabetes-related deaths.

National Glycohemoglobin Standardization Program (NGSP), certify that laboratory and point-of-care HbA1c testing methods are accurate and consistent with the Diabetes Control and Complications Trial (DCCT) standard.

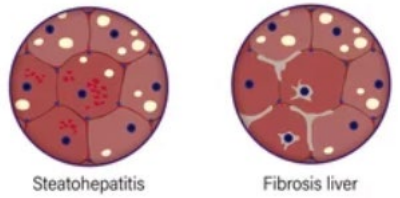
Examples of surrogate endpoints used for drug approvals - both VSE and RLSE

Disease	Patient population	Surrogate (VSE or RLSE)	Type of approval
Type 2 diabetes mellitus	Patients with type 2 diabetes mellitus	Serum hemoglobin A1C	Traditional
Gout	Patients with gout	Serum uric acid	Traditional
Hypercholesterolemia	Patients with homozygous familial hypercholesterolemia	Serum LDL cholesterol	Traditional
Polycystic kidney disease	Patients with autosomal dominant polycystic kidney disease +/- polycystic liver disease	Total kidney volume	Accelerated
Metabolic dysfunction associated steatohepatitis (MASH)	Precirrhotic NASH patients with liver fibrosis	Histopathologic findings of either 1) resolution of steatohepatitis… OR 2) improvement of fibrosis … OR 3) Both	Accelerated

FDA webpage Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure | FDA: https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure Content current as of: 08/29/2025

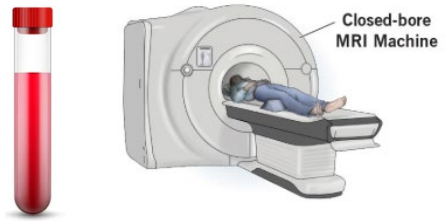
Question at hand for MASH:

Histology-based RLSE
that requires a liver biopsy



Transition

Non-invasive test (NIT)
-based RLSE



Thank you

Table 1. Points to consider when interpreting evidence from a surrogate endpoint.

Indirectness
If the relationship between the surrogate and the clinical (patient-important) outcome is not well-established or is uncertain, it can lead to indirectness in the evidence (less certainty with the apparent findings).
Lack of validation
If there is a lack of analytical validation studies demonstrating the credibility of the surrogate endpoint (*X*) in predicting clinical outcomes (*Y*), the quality of evidence might be rated down due to uncertainty.
Magnitude of effect
If the treatment effect on the surrogate endpoint is substantial but the effect on the clinical outcome is uncertain or smaller, this will reduce our certainty in the apparent findings.
Risk benefit balance
If using the surrogate endpoint as a basis for decision-making could lead to potential harm or inappropriate treatment decisions, a guideline panel is more likely to provide a conditional (weak) recommendation.
Uncertainty
The use of surrogate endpoints will introduce additional uncertainty into the evidence. If there is significant uncertainty regarding the relationship between the surrogate and clinical outcomes, the quality of evidence might be rated as less credible.

Surrogate Endpoint

Christensen, et al, Surrogate endpoints: a key concept in clinical epidemiology, Journal of Clinical Epidemiology, V 167, 2024