Supplementary Text and Tables
for
Proposed study designs for approval based on a surrogate endpoint and a post-marketing confirmatory study under FDA's accelerated approval regulations for disease modifying osteoarthritis drugs

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Definitions:

Clinical Endpoint: A characteristic or variable that reflects how a patient feels, functions, or survives.

Intermediate Clinical Endpoint: A measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality and is considered reasonably likely to predict the drug's effect on irreversible morbidity or mortality or other clinical benefit.

Surrogate Endpoint: A marker, such as 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.

Real-World Data (RWD): data relating to patient health status and/or the delivery of health care routinely collected. This includes data elements captured in a patient's electronic health record (EHR), in a hospital or insurance company's administrative and claims data, directly from patients or providers in the course of an observational study, from sources of patient-generated information outside of clinical settings (e.g., in-home monitoring devices, wearable technologies, fitness trackers), and in registries that support various aspects of care and research (derived from Berger et al, 2017[1]).

Real-World Evidence (RWE): evidence derived from RWD through the application of research methods. It conceptually allows for prospective capture of a wider variety of data, and utilization of study designs that are embedded in clinical practice but retain randomization (derived from Berger et al, 2017[1]).

Biomarker Nomenclature

One key issue which is often overlooked and which leads to much confusion and miscommunication is the lack of use of a common vocabulary that is tailor-made for a given purpose. To have and use the same description of key definitions is crucial for success[2]. The Biomarkers, Endpoints, and other Tools (BEST) resource[3] is a glossary that aims to capture distinctions between biomarkers and clinical assessments and to describe their distinct roles in biomedical research, clinical practice and medical product development. Other definitions have been developed and used such as BIPEDS (burden of disease, investigational, efficacy of intervention, diagnostic and safety biomarker classifications)[4, 5]. BIPEDS is a general categorization that is easy to remember, whereas BEST is a specialist nomenclature suited to clinical trial work with drugs. As seen from **Supplementary Table 1** (using examples from other disease areas), BIPEDS categories provide a broad, high-level categorization and the BEST categories provide subcategories of different types that correspond to each BIPEDS category. Both apply to biochemical and clinical intermediate endpoints. BEST also defines different levels of surrogate endpoints, which is extremely useful for generating regulatory documents and for assisting those discussions. **Supplementary Table 1** is extracted and amended from the BEST resource guide[3].

Supplementary Table 1. General use categories per BIPEDS[4, 5] and FDA (BEST)[3] nomenclature.

CATEGORY		DEFINITION	EXAMPLES
BIPEDS Category	**BEST Category**		
Burden of Disease		Biomarker associated with the extent of disease severity.	• Prostate-specific antigen (PSA) is the most widely utilized marker for evaluating disease burden of prostate cancer[6]. • Cancer antigen 125 (CA 125) may be used as a monitoring biomarker when assessing disease status or burden during and after treatment in patients with ovarian cancer[7-10].
Investigative		Biomarker does not yet meet the criteria for another category; it may be used in preclinical (animal) models for retrotranslational studies to understand disease mechanism.	• Any maker in development that does not meet criteria for any one of the other categories.
Prognostic	**Predictive biomarker**	Identify those subjects who are more prone than similar subjects, to experience a favorable or unfavorable effect after exposure to a drug or environmental agent (thus refers to the likelihood of treatment effects).	• Certain cystic fibrosis transmembrane conductance regulator (CFTR) mutations may be used in clinical trials evaluating treatment for cystic fibrosis, to select patients more likely to respond to particular treatments[11]. • Serological levels of HCV-RNA and its subtypes may be used to predict treatment response in patients with chronic hepatitis

			C[12, 13]
Prognostic	**Prognostic biomarker**	Identify probability of a clinical event, disease recurrence or progression in patients with the medical condition of interest (thus refers to the likelihood of disease-related events).	• Marker of Type III Collagen formation, PRO-C3, may be used to identify patients with significantly elevated PRO-C3 at an early stage of liver disease and thus most likely to develop into progressive liver fibrosis[14]. • BRCA1/2 mutations may be used when evaluating women with breast cancer, to assess the likelihood of a second breast cancer[15].
Prognostic	**Susceptibility/Risk biomarker**	Assessing the potential for developing a medical condition in a subject who does not currently have any symptoms	• Factor V Leiden may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop deep vein thrombosis (DVT)[16].
Efficacy of Intervention	**Monitoring biomarker**	Assessing the possible effect of exposure to a drug or an environmental agent.	• CTX-I has been validated by FDA under the 510(k) regulation and is used as a efficacy of intervention biomarker. Early changes in CTX-I, 4-8 weeks, predict changes after 1-2 years in bone mineral density (BMD) of the lumbar spine[17].
Efficacy of Intervention	**Pharmacodynamic/response biomarker**	• Pharmacodynamic or response biomarker: a biomarker that is used to show that a biological response has occurred • Display if a biological response has occurred after exposure to a drug or an environmental agent	• Serum LDL cholesterol may be used when evaluating patients with hypercholesterolemia, to assess response to a lipid-lowering agent or dietary changes[18]. • HbA1c may be used when evaluating patients with diabetes, to assess response to antihyperglycemic agents or lifestyle changes[19].
Efficacy of Intervention	**Surrogate endpoint**	Surrogate endpoint: an endpoint that is used in a clinical trial as a substitute for a direct measure of how a patient feels, functions or survives. A surrogate endpoint does not itself measure the clinical benefit of primary interest, but rather is expected to predict	• HIV viral load. • Lowering blood pressure has repeatedly been shown, with a wide variety of drugs, to reduce the incidence of stroke and cardiovascular disease in people with

		clinical benefit or harm based on epidemiological, therapeutic, pathophysiological or other scientific evidence.	hypertension. • Serum urate in gout[20]
Diagnostic	**Diagnostic biomarker**	• Differentiate disease from non-disease states • Detect or confirm the presence of a disease or medical condition of interest. • Identify individuals with a subtype of the medical condition of interest.	• Blood glucose levels may be used to identify patients with Type 2 diabetes mellitus[21]. • Gene expression may be used to segregate patients with diffuse large B-cell lymphoma into subgroups with different tumor cell of origin signatures[22].
Diagnostic	**Monitoring biomarker**	• Monitoring status of a medical condition by repeated measurements. • Monitoring biomarker: a biomarker that is measured serially and used to detect a change in the degree or extent of disease.	• Marker of Type III Collagen formation, PRO-C3, may be used when assessing status and progression/regression of liver fibrosis patients. • DXA for osteoporosis
Safety	**Safety**	Measure before and/or after exposure to a drug or environmental agent to assess possible toxicity as an adverse effect	• Hepatic aminotransferases and bilirubin may be used as safety biomarkers when evaluating potential hepatotoxicity[23]. • Serum creatinine may be used when evaluating patients on drugs that affect kidney function to monitor for nephrotoxicity[24].

BIPEDS: burden of disease, investigative, prognostic, efficacy of intervention, diagnostic and safety. Data from REFs[3-5].

What is a surrogate?

The FDA may grant accelerated approval for a drug that has demonstrated, in adequate and well-controlled trials, an effect on a "surrogate endpoint" that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit"[25, 26]. Based on FDA guidance on accelerated approvals, "a surrogate endpoint is a marker, such as 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"[27]. Three levels of surrogacy are recognized[3, 27]: a "validated" surrogate endpoint that has been shown to predict or correlate with clinical benefit (and that could therefore be used as a basis for traditional approval); a "reasonably likely" surrogate endpoint that correlates with clinical benefit (and that may be used for accelerated approval but with a post-approval confirmatory study) but is without sufficient clinical data to show that it is a validated surrogate endpoint; or, based on the Biomarkers, Endpoints, and other Tools (BEST) nomenclature[3], a "candidate" surrogate endpoint that is still under evaluation for its ability to predict clinical benefit (see **Supplementary Table 2** for biomarker examples).

Supplementary Table 2. Different levels of surrogacy based on the BEST resource guide[3].

Endpoint	Definition	Example
Validated surrogate endpoint	• An endpoint supported by a clear mechanistic rational 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.	• Low-density lipoprotein (LDL) cholesterol reduction is a validated surrogate endpoint for reduction of cardiovascular events and has been used as the basis for approval of statins and other LDL-lowering drugs.
Reasonably likely surrogate endpoint	• An endpoint supported by clear mechanistic and/or epidemiological 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, addition trial data, assessing the effect of the intervention of the clinical beneficial endpoint of interest will be collected in the post-marketing setting to verify whether an effect on the reasonable likely surrogate actually predicts benefit in the specific context under study.	• Outcomes of 6-month follow-up treatment i.e., sputum culture status and infection relapse rate, have been considered reasonably likely to predict the resolution of pulmonary tuberculosis and have supported accelerated approval of drugs to treat tuberculosis.
Candidate surrogate endpoint	• An endpoint still under evaluation for its ability to predict clinical benefit.	• Early fungicidal activity is currently proposed as a candidate surrogate endpoint for all-cause mortality in cryptococcal meningitis[28].

To aid in this determination, it is helpful to consider the following:

1. How much do changes in the surrogate endpoint reflect changes in the clinical outcome or the probability of the clinical outcome occurring?

2. Is there an understanding of the required degree and timing of change in the surrogate endpoint that represents a clinically meaningful change or absolute change in the clinical outcome?

3. If a threshold for change is selected, what is the basis for its selection, its sensitivity and specificity?

4. Is the change in the threshold stable or does it only occur for a short time? Would timing of sample collection be feasible?

The surrogate endpoint should be based on a comprehensive understanding of the disease process and under ideal circumstances, in the causal pathway of the disease. For a complex disease such as OA, which involves the whole joint and a complicated pathogenesis of bone, cartilage, and synovium, providing evidence of a link to the causal pathway of disease may not be easy. Cartilage has often been discussed as the common denominator, and central for the disease, but biomarkers of bone and synovial pathology may be equally viable, if they are related to outcome. These sentiments are acknowledged by the FDA, in their prior 1999 guidance document:

> Structure is a critical component of OA assessment, but the relationships between structure and pain and/or function and between structure and future outcomes (e.g., arthroplasty) are not well developed. At a minimum, cartilage destruction is a necessary but not sufficient prerequisite for arthroplasty. Additionally, OA may be asymptomatic early on, complicating the relationship between structure and outcome. Numerous epidemiological studies are underway to try to clarify these relationships. Because OA is a disease of all the tissues in the joints, not just the cartilage, measurements of *structure* need to be seen broadly and capture important anatomic features, such as osteophytes or ligamentous instability, in addition to cartilage loss[29].

The majority of surrogates used in trials in other fields and anticipated for use in OA are of the "reasonably likely" surrogate endpoint variety. The determination of "reasonably likely" is based on a synthesis of both statistical reasoning and clinical insight[30, 31] that satisfy the criteria in **Supplementary Table 3**. Interestingly, to date the FDA has accepted serum uric acid level as the primary efficacy endpoint for approval of treatments for hyperuricemia associated with gout[20]. These recommendations are based on informal qualification of this biomarker--long-term cohort studies demonstrating an improvement of clinical disease with the lowering of serum uric acid levels in patients with gout. Interestingly, no therapies for the treatment of hyperuricemia associated with gout have been required to demonstrate a statistically significant effect on clinical outcomes "because of the duration of trials necessary to evaluate such a treatment effect"[20].

Supplementary Table 3. Evidence for validating a "reasonably likely" surrogate endpoint (based on Fleming et al. 2005)[30].

Criteria for reasonably likely surrogacy
• Considerable clinical evidence that the intervention's effect on the surrogate endpoint will accurately represent the intervention's effect on what is thought to be the predominant mechanism(s) through which the disease process (OA) induces risk of clinically tangible events.
• Considerable clinical evidence that the experimental intervention does not have important adverse effects on the clinical efficacy endpoints that would not be captured by the outcome measure.
• Statistical analyses suggest that the net effect of the intervention on the true clinical efficacy measure is consistent with what would be predicted by the level of effect on the outcome measure.
• The targeted effect on the outcome measure is sufficiently strong and durable that, based on the relationships specified by the criteria above, this is reasonably likely to predict meaningful clinical benefit on clinical efficacy measures

Development hurdles in OA compared to other diseases

Drug development in other disease indications, such as type II diabetes (T2D), involve large outcome studies with more than 10000 patients, not as part of a Subpart H approval process, but still as a post-approval commitment to understand potential benefits of lowering Hba1c and drug-induced potential harms. (**Supplementary Table 4**) Drug development in osteoporosis, like OA, is to some extent also focused on the skeletal system and based on radiographic analysis. Drug approval relies exclusively on a failure of tissue (fracture), without an assessment of a PRO. The phase 3 studies in osteoporosis have been very large, with more than 8000 patients included. Interestingly, the phase 2 studies in osteoporosis rely on imaging techniques that measure the local amount of bone (bone mineral density of the lumbar spine), whereas the phase 3 studies are based on tissue failure assessed by radiograph to investigate fractures in the lumbar spine, as well as fractures at other skeletal sites in later studies. This connection between the assessments using imaging biomarkers in phase 2, which translates to tissue failure in phase 3, may apply to OA.

Supplementary Table 4. Instructive representative trials.

DISEASE	PHASE 2B	PHASE 3	POST-APPROVAL PHASE 4 OR SUBPART H STUDY
Osteoporosis Alendronate, Zoledronic acid, Teriparatide, calcitonin, Abaloparatide, and Denosumab	REFS: [32] N: 200-400 patients Endpoint: Imaging by X-ray, BMD Duration: 6 months to 2 years	REFS: [33-38] N: 2000-8000 patients Endpoint: Fractures determined by X-ray Duration: 1.5 to 3 years	Unnecessary since incidence of fracture is a hard outcome reflecting “survival” of adequate structural bone integrity.
NASH Elafibrinor, Cenicriviroc, Obetocolic acid	REFS: [39-41] N: 200-400 patients Endpoint: Histology by liver biopsy Duration: 6 months to a year	Obetocolic acid, NCT02548351, Elafibrinor, NCT02704403 Cenicriviroc, NCT03028740 N: 2000-2400 patients Conditional approval endpoint: Histology by liver biopsy Duration: 2 years	Subpart H N: 2000-2400 patient Outcome measures: improvement or resolution of NASH without fibrosis worsening (a strong predictor of liver-related deaths) and death Duration 4-5 years
T2D GLP-1s, SGLT2s, PPARs	REFS: [42-44] N: 200-to 450 patients Endpoint: HbA1c Duration: 3-6 months	REFS: [45-50] N: 400 to 1500 patients Endpoint: HbA1c Duration: 6 months to 2 years	REFS: [51-55] **OUTCOME STUDY** N:3300- to 10500 patients years Endpoint: MACE 3, cardiovascular outcome Duration: 1-3 years
OA Calcitonin, Sprifermin (FGF-18), Risedronate, Cindunistat	REFS: [56-59] and NCT01919164 N: 200-550-1500 patients Endpoints: Structure by Imaging such as X-ray or MRI Function: PRO such as WOMAC Duration: 6 months to a year or more	REFS: [60, 61] N: 1000-2500 patients Endpoints: Structure by imaging such as imaging or MRI Function: PRO, such as WOMAC Duration: 2 years or more	 N: 1000-2000 patients Endpoints: The topic of this discussion

NASH=non-alcoholic steatohepatitis; T2D=type II diabetes; MACE 3=three-point major adverse cardiovascular events; OA=osteoarthritis; MRI=magnetic resonance imaging; PRO=patient-reported outcome; WOMAC=Western Ontario McMaster Universities Osteoarthritis Index

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