**Definition 1**

*A biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic; therapeutic; pathophysiologic; or other scientific evidence.*

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| **Theme** | **Free text comment** | **Response from project team if any** |
| Not inclusive | * It's not only biomarkers that can act as surrogate endpoints. Suggest enlarging by "A biomarker; intermediate or any other endpoint" * not exclusively a biomarker * In oncology; does not address tumour response as a surrogate for survival; for example; since response is not necessarily a biomarker. * Seems quite restrictive as not all surrogates are biomarkers |  |
| Other limitations | * Completely confusing based on the abused term "clinical" benefit. Clinician Reported Outcomes based on clinician observations are SURROGATES yet often presented as "clinical" endpoint - really really confusing for readers |  |
| Context of item importance | * A fair description of an unvalidated surrogate outcome. Surrogates can never be endpoints! * almost perfect definition in my view - without "based on epidemiologic; therapeutic; pathophysiologic; or other scientific evidence" |  |
| Suggested modification | * the evidence should be experimental (statistical evidence of surrogacy) more than anything; event if the epidemiologic and pathophysiologic evidence is also important. I am not sur I understand correctly the statement * I would add two mandatory statements like: 1) What is the mechanist evidence that surrogacy is acceptable? 2) what is and how was derived the relation that enables to compute the size of effect on the final outcome from the effect on the surrogate? * It will be better to provide an evidence for their explanations |  |
| Comments on scale | * The headings on this page do not match the definitions of the nine categories given at the top of the page. * scale above doesn’t match instructions * the response should be continuum of complete and inclusive rather than importance continuum. Should complete and inclusive be the only response of interest? This is the traditional NIH definition and for this reason perhaps it should not be changed? |  |

**Definition 2**

*A laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels; functions; or survives and is expected to predict the effect of the therapy*

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| **Theme** | **Free text comment** | **Response from project team if any** |
| Not inclusive | * Clinical SIGNS often ignored as surrogates which they ARE and since they are measured by clinicians often presented as "clinical endpoints" but not direct patient endpoints * a surrogate could be any information (e.g., speech or imaging); also and outcome in trials on prevention * not exclusively in therapeutic trials * should it just be therapeutic trials? e.g. What about diagnostic studies. I like that it includes a physical sign as. It depends on how one defines a biomarker. Can we suggest a definition? * In oncology; does not address tumour response as a surrogate for survival; for example; since response is not a lab value.. * Again; not all surrogates are lab measures of physical signs * This mixes the definition of a surrogate and the definition of a clinical endpoint. Effect of therapy is too unspecific |  |
| Modification to item | * predict the effect therapy "ON THE PATIENT-RELEVANT ENDPOINT" * I would add two mandatory statements like: 1) What is the mechanist evidence that surrogacy is acceptable? 2) what is and how was derived the relation that enables to compute the size of effect on the final outcome from the effect on the surrogate? |  |
| Other comments | * Also relevant to vaccine trials and other prophylactic interventions * This statement seems like a confusion of quantitative and qualitative measures - feels; functions and survives are three very different things. |  |

**Definition 3**

*A response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint.*

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| **Theme** | **Free text comment** | **Response from project team if any** |
| Lacks clarity | * Not written clearly at all * too complicated * requires a plain English explanation * I cannot rate. It is a spurious statement. User of surrogate guess it is true but cannot support it; except from gut feeling * Too statistical - it’s true; but clinicians won't understand this. * Not sure what is meant by response variable - any kind of variable hat records a change in a patient’s condition or a questionnaire response. If the former this definition effectively includes all the others so is the most general |  |
| Other comments | * The problem with a null hypothesis reliance is that patients reading the study will mostly not understand the process here. * This also refers to ANALYIS of treatment effects and not to WHAT Is measured. A surrogate can be used in an observational study as well which does not involve treatment effects. Separate issue of "what is a surrogate" vs how it is used * Theoretically correct; but probably not of great help in practice. * the concept of surrogacy is unrelated to statistical testing * This could corresponds to a non eligible confounder * statistical Prentice type definition * the quantification of the expected benefit on the clinically relevant endpoint is also important |  |

**Definition 4**

*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.*

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| **Theme** | **Free text comment** | **Response from project team if any** |
| Modification to item | * My concern with this statement is the verb "predict". In surrogacy setting, predict means that there is a validated relation that enables to infer the size of the benefit on clinical outcome (the 'final' outcome) from the effect on the surrogate. Most of the tie such a function does not exist or is based on correlations (unreliable alternative; further often measured in different settings). Thus, instead of 'predict'; I suggest 'guess' in this statement. * “is expected to predict” is not specific enough. Suggest adding in "has been shown to reliably predict". |  |
| Other comments | * This gets to HOW surrogate is used in a trial whereas second definition above refers to WHAT Is measured; this gets to HOW it is used to measure treatment effects |  |

**Definition 5**

*A biomarker or intermediate outcome used to substitute for a patient or participant relevant final outcome (i.e., severe morbidity; health related quality of life or mortality) and reliably predicts benefit or harm based on epidemiologic; therapeutic; pathophysiologic; or other scientific evidence*

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| **Theme** | **Free text comment** | **Response from project team if any** |
| Context of item importance | * Seems restrictive as not all trials seek to provide information about severe morbidity; HRQoL or death * They may be all valid or not depending on whether or not there is a proper validation study... * A fair description of a validated surrogate outcome |  |
| Modification to item | * ...predicts... probably not precise enough. How about " and reliably predicts"? * Without the text "based on epidemiologic; therapeutic; pathophysiologic; or other scientific evidence" very useful * predicts benefit or harm could be improved (i.e. more accurate) if changed to something like "is expected to predict" or "is likely to predict" * Used IN CLINICAL TRIALS to substitute...? ...and IS EXPECTED TO PREDICT CLINICAL benefit or harm OF TREATMENT? Provide example of biomarker and example of intermediate outcome? * My concern with this statement is the verb "predict". In surrogacy setting, predict means that there is a validated relation that enables to infer the size of the benefit on clinical outcome (the 'final' outcome) from the effect on the surrogate. Most of the tie such a function does not exist or is based on correlations (unreliable alternative; further often measured in different settings). Thus, instead of 'predict'; I suggest 'guess' in this statement. | “reliably” added to the definition |
| Other comments | * The term "intermediate" is not well understood and would include patient symptoms and function not just distal measures of quality of life which is distinct from direct measures of symptoms * there's so much variance for each of these points that I can't answer * a surrogate is really designed for the context of comparative trials |  |