**S2 File: Examples of assessing indirectness of evidence from preclinical animal studies**

**The population or the induced disease in the studies differs substantially from the population or the disease in which we are interested**

* Matching preclinical conditions to clinical setting (also with regard to physiological derangement; i.e. should ideally be similar)
* Assessment of multiple manifestations of disease phenotype
* Species: multiple species tested; comparable results between different species
* Animal model/disease: similarity of disease in clinical setting, e.g. how is disease induced in the animals
* Model match to human manifestation of disease, interventions and sex, age and co-morbidities of patients in clinical setting
* Characterization of animal properties at baseline
* Co-morbidities

**The Intervention of the studies differs substantially from intervention in which we are interested**

* Optimization of complex treatment parameters
* Matching timing of treatment delivery to clinical setting
* Matching route/method of treatment delivery to clinical setting
* Definition of treatment
* Faithful delivery of intended treatment
* Theoretical relationship between experimental operations/interventions and clinical scenario
* Treatment response along mechanistic pathway
* Use of validated assay for molecular pathways assessment
* Treatment interactions with clinically relevant co-morbidities

**The Comparison of the studies differs substantially from comparison in which we are interested**

* Appropriate control group
* Comparability of control group characteristics to those of previous studies
* Indirect comparisons

**The Outcome of the studies differs substantially from outcome in which we are interested**

* Degree of characterization and validity of outcome measure chosen
* Assessment of outcome at late/clinically relevant time points