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**Title:** OMERACT Filter 2.1: elaboration of the conceptual framework for outcome measurement in health intervention studies

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JAS has received consultant fees from Crealta/Horizon, Fidia, UBM LLC, Medscape, WebMD, the National Institutes of Health and the American College of Rheumatology. JAS is a member of the Veterans Affairs Rheumatology Field Advisory Committee. JAS is the editor and the Director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis. JAS served as a member of the American College of Rheumatology's (ACR) Annual Meeting Planning Committee (AMPC) and Quality of Care Committees, the Chair of the ACR Meet-the-Professor, Workshop and Study Group Subcommittee and the co-chair of the ACR Criteria and Response Criteria subcommittee.

LM is a Principal Investigator on the Australian Rheumatology Association Database that has received arms-length funding from 8 companies.

PT has received honoraria for quality of life consultancy with BMS, chairs data safety monitoring boards for Chelsea and UCB, has mandated for the FDA, co-chairs an industry board of 6 companies (Abbott, BMS, Merck, Roche, Schering Plough, UCB) for a biologics registry of the Ontario Rheumatology Association [Ontario Biologics Research Initiative (arms-length registry that independently collects information)], received a grant from the Canadian Institutes of Health Research (CIHR) matched by funding from these pharmaceutical companies); and receives an honorarium from the CIHR grant.

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**A short running head:**

OMERACT Filter 2.1 Framework

## Abstract

**Background & Objective:** The OMERACT Filter 2.0 framework was developed in 2014 to aid core outcome set development by describing the full universe of ‘measurable aspects of health conditions’ from which core domains can be selected. This paper provides elaborations and updated concepts (OMERACT Filter 2.1).

**Methods:** At OMERACT 2018, we discussed challenges in the framework application caused by unclear or ambiguous wording and terms, and incompletely developed concepts.

**Results:** The updated OMERACT Filter 2.1 framework makes benefits and harms explicit, clarifies concepts, and improves naming of various terms.

**Conclusion:** We expect that the Filter 2.1 framework will improve the process of core set development.

## Introduction

Since 1992, The Outcome Measures in Rheumatology (OMERACT) initiative has successfully improved outcome measurement for many rheumatologic conditions by developing widely endorsed ‘core outcome measurement sets’ that include a minimum set of outcome measures to be reported in all randomized controlled trials (RCTs) in a given health condition. As OMERACT grew, its framework and process to develop core domain sets and core outcome measurement sets needed clarification. This was provided by the OMERACT Filter 2.0 Framework and process published in 2014.<sup>(1)</sup> Briefly, to improve content validity of core sets, Filter 2.0 intended to describe the full universe of ‘measurable aspects of health conditions’ by introducing four ‘Core Areas’ in which all domains of measurement would fall: Death, Life Impact, Resource Use and Pathophysiological Manifestations (Figure 1). Core set developers were required to choose at least one domain in each area, except for the area of

resource use, which was considered optional. Since its launch Filter 2.0 has been successfully applied to the development of several core sets both within- and outside OMERACT (2-8). However, there are challenges in application caused by ambiguous wording and terms and incompletely specified concepts. In this paper, the OMERACT Executive proposes a further elaboration and update of the Framework. As such, it is not a product of consensus at the conference, but its utility will continue to be evaluated by the users, i.e. the OMERACT community.

[INSERT FIGURE 1]

### Challenges in the original framework

In the original framework (Figure 1), adverse events and context ‘dangled’ underneath the areas and domains with examples. During the first development of the framework we realized that these concepts were essential, but struggled to identify the optimal way to include them. In addition, many users raised concerns with the core areas of Death (as being distinct from an adverse event) and Pathophysiological Manifestations. Death is particularly a problem for core sets in health conditions that do not necessarily impact survival; selection of domains for Pathophysiological Manifestations are a problem when the health condition is nonspecific or no clear pathophysiology has been recognized, e.g. fibromyalgia or non-specific low back pain. Finally, proper placement of domains within the areas of Life Impact or Pathophysiological Manifestations can be difficult or arbitrary, with some domains appearing to fit into both due to lack of clear criteria for placement.

### Improving the terminology and ordering of the Core Areas

To enable improvement, we must first return to the primary purpose of the framework. A core domain set specifies the domains that should always be measured in a trial of an

intervention targeted at a health condition, regardless of whether the primary study question includes these domains (1). The framework is designed to help the development of core sets that meet minimum requirements of content validity. Each core area in the framework has a specific role, and together they contain the whole ‘universe’ of domains (concepts) that one could conceivably measure to assess the effects of an intervention. For each core set, OMERACT helps to ensure content validity by mandating the choice of at least one domain in each area (except for societal/resource use which is optional). We have reordered the areas to better align them with existing biopsychosocial and biomedical models (9, 10). The Framework intends to complement these models by its focus on the choice of domains to optimize breadth and content of a core set. A key clarification discussed in more detail below is that beneficial and harmful effects of interventions are measured in the same domain space: for example, methotrexate can increase participation through improvements in rheumatoid arthritis activity, but can also decrease participation due to severe intermittent nausea. (Figure 2)

[INSERT FIGURE 2]

### Pathophysiology: Manifestations/Abnormalities

A health condition manifests itself by abnormal physiology (pathophysiology) as symptoms, signs, biomarker signals, or events. These include for example fever, fatigue, oral ulcers, rash, range of motion limitation, anemia, hematuria, erosive damage, etc. All of these can be seen as manifestations of the underlying health condition (disease, morbidity) and can be distinguished from their impact (see below). A better term for the concept is Pathophysiology, and the core area term can be shortened to ‘Manifestations’. In the

International Classification of Function (ICF) Framework, such manifestations are captured under 'body structures' and 'body functions' (10). To fully assess an intervention, we think it is essential that its effects on the underlying pathophysiology are captured; hence this is a core area. In many conditions, the pathophysiology may not be fully elucidated, so the selection of domain(s) for this area must be a 'best effort'. Furthermore, the core domain set will need to be regularly updated to track developments in understanding. In some health conditions, pathophysiology is left undefined 'by definition' (e.g. nonspecific low back pain) or it is heterogeneous (e.g. 'shoulder disorders'). In such cases, the development group has two options: 1) they can decide to place domain(s) in this area chosen to reflect the main manifestation(s) (e.g. 'pain, 'renal function'); or 2) they leave the core set incomplete, to be further specified per trial. In the latter case, the core set can state that trialists have to choose a domain that aligns with the manifestations that are the target of intervention in that RCT. In both cases, the area of pathophysiological manifestations will measure at least one domain.

#### [Impact: Life Impact, Death/Lifespan and Societal/Resource Use](#)

The description of outcome as 'how a patient feels, functions or survives' has been ascribed to Temple (11), and is frequently quoted in documents of the US Food and Drug Administration (12). It certainly concurs with Fries et al.'s seminal work on the Health Assessment Questionnaire: 'A patient certainly desires to be free of pain, functioning normally, experiencing minimal treatment toxicity, and financially solvent' (13). In the Framework, this is entitled "Impact" and encompasses both the impact on the life lived (feeling and functioning), and on lifespan (survival, mortality). For patients, usually it is not, or not only the manifestation but its impact that is relevant and should be measured. Life

impact is captured by concepts such as well-being, health perception, utility, and by the ICF categories of activities and participation. It also largely overlaps with the concept or global domain of 'health-related quality of life', and ability to live and function independently.

Although such a global domain can be useful, OMERACT encourages developers to try and choose more specific domains that better align with the lived experience of the condition for which the core set is being developed. So for example, fatigue and sleep loss have a major impact on quality of life in RA, as does social isolation in psoriasis, and weight gain in osteoarthritis; if such impacts are deemed core, it may make more sense to propose these as core domains rather than to capture them under a generic 'quality of life' domain.

To date, a symptom or event has frequently been taken as a proxy for its impact, but this is usually suboptimal. For example, core set developers could consider the quality and intensity of pain as the manifestation, but choose not to include impact of pain as a separate domain (e.g., 'pain interference'). Pain intensity would then be seen to represent both pathophysiology and life impact. Using events as proxy for impact is more problematic. For example 'bone fracture' is a pathophysiologic manifestation, but its impact can be very small or very large, and span across many different concepts, e.g. inability to perform key activities of daily living that differ depending on the location of the fracture or the way it has healed. Choosing domains that directly address the impact(s) is preferable and recommended in this framework.

Death/Lifespan as target of intervention is pertinent in potentially fatal health conditions such as vasculitis, systemic sclerosis, and lupus erythematosus. In most other rheumatologic conditions, in the context of a clinical trial death is only a rare adverse event; in core sets for such conditions this core area will simply be filled by the domain 'count of deaths' (see also

next section: benefit and harm). The term lifespan was added to capture the duration of living rather than only focusing on the discrete event of death.

The impact of health conditions on individuals also translates to impact on society: these are expressed as health care utilization leading to so-called 'direct' costs, and productivity losses leading to 'indirect' costs. Although clearly important, we maintain OMERACT's original choice to regard this area as optional, meaning that developers are not mandated to choose a domain from this area in their core set.

### Benefit and Harm: intended and unintended effects of intervention

To study the effects of an intervention, our focus is on measuring changes (improvement or deterioration) or counting events (good or bad); however, apart from the intervention such changes can be due to the natural course of the disease/health condition, or to unrelated comorbidities. Only in a properly designed clinical trial can causal inferences be made with confidence, and only at the group level: randomization creates groups with similar prognostic characteristics, and differences above random error (in mean change or the occurrence of events) can then be ascribed to the interventions administered.(14)

Interventions are targeted to reduce, eliminate, or prevent the manifestations of the health condition or their impact. When the intervention has beneficial effects, we say it is successful. However, interventions can also cause harm by inducing new manifestations or worsening existing ones. The original framework paper already stated: 'Benefit and harm can be regarded as opposite directions on one "impact scale," measurable in one of the core areas.' This is further clarified in the current elaboration (Figure 2,3): the framework areas allow for domains that can measure benefit, harm, or both, resulting in a 'net effect'. For example, an intervention can increase work/family/leisure participation due to decreased

pain and stiffness (benefit), but at the same time decrease participation due to increased fatigue (harm). Or in the case of glucocorticoids and osteoporosis, these agents have negative effects on bone, but in rheumatoid arthritis they also counteract the negative effects of inflammation on bone.

### Example Domains

[INSERT FIGURE 3]

In Figure 3, the concepts of benefit and harm are again distinguished and example domains are included with each. Note that most current core sets focus on benefit, and the Framework does not require core set developers to include separate benefit and harm domains. For Manifestations, we stress that symptoms and signs of the health condition *per se* belong here, as target of benefit; their impact (if deemed core) should be separately measured and placed under life impact. For example, in polymyalgia rheumatica manifestations included only systemic inflammation (15), but in psoriatic arthritis it also included separate domains for musculoskeletal and skin disease activity.(16) For Life Impact both included the core domains of pain and physical function, to which polymyalgia added stiffness, and psoriatic arthritis patient global assessment, fatigue, and health-related quality of life. Adverse event reporting is mandatory in trials, and the requirements for reporting are best seen as separate from the development of a core set. Nevertheless, all such events can be conceptually placed in core areas, and where necessary, specific core domains of harm can be specified. For example, developers could decide to include ‘infection’ as a core domain.

For Impact, historically effort has been targeted at defining the core domains necessary to document benefit. For harm, it quickly became clear that adverse events were not

adequately integrated into the model. At OMERACT 2018, pivotal discussions between stakeholders were held at a pre-conference meeting (17). One key finding spurred the current elaboration of the framework: patients explained that they usually did not experience adverse effects or harm from treatment as a series of discrete events that could be captured according to regulatory guidelines (18). Instead, they described harm as an intermittent or continuous discomfort 'in the background', often not serious enough to warrant priority in a consultation with their physician, but nevertheless significantly impacting well-being and participation as well as potentially choice of therapy.(17) For example, a patient described her days following methotrexate ingestion as 'a feeling of nausea, fatigue, being generally unwell that hinders undertaking activities'. Currently this potential core domain of harm is not captured at all, or only indirectly through global patient assessments of health. We have now added it under the label 'unintended impact of treatment on functioning/participation'. We expect this domain to become core in many future core sets. It has already been picked up in psoriatic arthritis as 'treatment burden' and placed in the 'research agenda' ring of the OMERACT onion.(16,19) In addition, and especially pertinent for patients with a chronic condition, the concept 'burden of treatment' has been introduced to describe a patient's 'workload' in terms of time and effort to adhere to treatment regimens (including taking drugs), visiting health professionals, and other health-related activities.(20,21) We now add the burden on personal finances that can also constitute real life impacts for patients, including their ability to continue a course of treatment.

Regarding the area of Death/Lifespan, OMERACT acknowledges that for many health conditions, death is very rare in clinical trials. However, OMERACT Core Outcome Sets should follow clinical trial reporting guidelines that mandate reporting the number of deaths as

adverse event. Our current thinking is shown by the distinction between ‘Survival’ as a domain to show benefit of interventions for conditions that are potentially fatal, and ‘Mortality’ for the other conditions, where death is likely only relevant as an adverse event in the clinical trial setting. The term lifespan was chosen to describe the duration of living rather than focusing on the discrete event of death.

For Societal Impact, the domain of costs is placed in between benefit and harm.

Traditionally, costs are seen as ‘harm’ to be traded against the benefits of the intervention. However, cost could also be the target of an intervention, and decreases seen as benefit.

### Domain selection process

The process to select domains is described in the OMERACT Handbook (19), and updated in the OMERACT 2018 conference proceedings (22). Briefly, core set developers must name at least one domain in each of the areas: Manifestations, Life Impact, and Death/Lifespan.

Guidance has been developed for placement of domains in an area. If properly supported by arguments and agreed to by the OMERACT community, domains can be shared between areas (as described above) and choices for domains can be made on the benefit and on the harm side (as in the case of Mortality for non-fatal conditions).

### Setting; Personal and Environmental Context

In the original framework paper we stated: ‘Core set developers need to specify the setting of the core set, and consider if any contextual factors need to be documented in every trial’.

Setting (or scope) includes the health condition, target population for the intervention, type of intervention, and so on. Contextual factors can be defined as those that are not the primary object of research but that may influence the results or the interpretation of the results. These include potential confounders and effect modifiers (most of which should be

eliminated by randomization), as well as factors that define the generalizability of the study findings.’(1) In the current elaboration, the label has been made more specific by following the ICF terminology and adding ‘personal and environmental’, but otherwise things are unchanged. An OMERACT special interest group is exploring the process of selecting important and core contextual factors for a core set (23). Discussions are ongoing, but we posit that consideration of context is important in at least three phases: 1) domain selection; 2) instrument selection (for correct interpretation of measurements); and 3) consideration of other factors that should be included as effect modifiers/confounders in the analysis and interpretation of the trial.

Box 1 outlines the changes incorporated into the revised Framework as described above.

[INSERT Box 1]

## Conclusion

The OMERACT Filter 2.0 framework and process has been widely quoted and implemented both within- and outside OMERACT. We hope the current elaboration, termed ‘OMERACT Filter 2.1’ clarifies and helps to solve problems encountered by users.

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## Figure Legends

Figure 1. The OMERACT Filter 2.0 Framework as published in 2014 (1).

Figure 2. Updated OMERACT Filter 2.1 Framework. All measurable aspects of health conditions (diseases) are captured in the core areas. These contain all the domains in which effects of an intervention can be measured. Most core set developers focus on identifying core domains for intended benefits, i.e. improvements on disease-related manifestations and impacts. But conceptually the areas can also be used to define core harm domains where required, i.e. the unintended effects, e.g. worsening of comorbidity and negative impacts. Core domain sets are defined for a specific context, and should contain at least one domain from each of the core areas (societal/resource use is optional).

Figure 3. Example domains within the updated OMERACT Filter 2.1 Framework. Mandatory adverse event reporting is not within the scope of a core domain set, except for the area of

Death/Lifespan in settings where death is a rare event. Societal and resources use are outside of the shaded boxes as the same indicator such as cost can represent both intended effects and harms.