**Title:** **An OMERACT Initiative Towards Consensus to Identify and Characterize Candidate Contextual Factors: Report from the Contextual Factors Working Group**

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*The Contextual Factors Methods Group (CFMG) was formed to address a recommendation in the Handbook 2.0, to investigate factors that may significantly influence interpretation of a (new) patient-reported outcome. We shared our research in a special interest group (SIG) at OMERACT 2016, gaining useful input to inform a future research agenda.*

**ABSTRACT (249 words)**

*Background:* The importance of contextual factors (CF) for appropriate patient-specific care is widely acknowledged. However, evidence in clinical trials on how CFs influence outcomes remain sparse. The OMERACT handbook 2014 introduced the role of CFs in outcome assessment and defined them as “potential confounders and/or effect modifiers of outcomes in randomized controlled trials (RCT)”. Subsequently the CF Methods Group (CFMG) was formed to develop guidance on how to address CFs in clinical trials.

*Methods:* First, the CFMG conducted an email-survey of OMERACT working groups (WGs), to explore how they had addressed CFs in outcome measurement so far. The results facilitated an informed discussion at the OMERACT 2016 CFMG Special Interest Group (SIG) session, with the aim to gain preliminary consensus among stakeholders regarding a operational definition of CFs and to gain a first selection of potentially relevant CFs.

*Results:* The survey revealed that the WGs had mostly used the OMERACT handbook and/or the ICF definition. However, significant heterogeneity was found in the methods used to identify, refine and categorize CF-candidates. The SIG-participants agreed on using the ICF as framework along with the OMERACT handbook definition. A list with twenty-eight variables was collected including person-related, physical and social environment. Recommendations from the SIG guided the CFMG to formulate three preliminary projects on how to identify and analyze CFs.

*Conclusion:* New methods are urgently needed to assist researchers to identify and characterize CFs that significantly influence the interpretation of results in clinical trials. The CFMG defined first steps to develop further guidance.

**Key Indexing Terms**

Contextual, Rheumatology, OMERACT, Patient Reported Outcomes, Randomized Controlled Trials, Effect Modifier

Text box: New items to be found in this work:

* Contextual factors (CFs), acting as effect modifiers, may influence the intervention outcomes of randomized clinical trials (RCTs) studies in rheumatology.
* Methods to identify, measure, and test potential core contextual factors are needed.
* The OMERACT - Contextual Factors Methods Working Group (CFMG) developed a research agenda to provide guidance on the fundamental steps to identify CFs that are essential for interpreting results in the setting of an RCT in rheumatology.

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Identifying contextual factors

**Word count:** 1484

**Background**

The importance of contextual factors for appropriate, patient-specific care, especially in chronic conditions such as rheumatic diseases, is widely acknowledged (1-4). CFs may include sociodemographics, person-related factors, physical and social environments (5). However, despite logical arguments and clinical experience, evidence in clinical trials on how CFs influence outcomes remained sparse (6). Most researchers agree that CFs, such as age, gender and duration of disease, should be identified in rheumatic RCTs to check if an unequal distribution of CFs despite randomization could confound the outcome. However little is known concerning the influence of person-related, physical or social environment.

In addition, CFs such as phenotypical subgroups (e.g. differences in disease subgroups, previous pharmacological management or personal or environmental characteristics) can distort the net benefit (or harm), and thus have potential to act as “effect modifiers”(7). **Figure 1** illustrates a hypothetical RCT example where patients were randomized to either active intervention or placebo. The trial illustrates that these interventions are equally effective. However, *re-analyzing the data set and stratifying the analysis according to a potential CF revealed a divergent efficacy pattern* in favor of the active intervention compared to the placebo in the CF-positive subgroup. For those who design trials, CFs acting as effect modifiers can provide a quantitative perspective elucidating a difference in effect (i.e. net-benefit) between subgroups. This has important implications for clinical practice and policy-making, such as calling for more individualized treatment strategies(8).

Acknowledging the need to integrate CFs into the outcome measurement in rheumatic RCTs, in 2012 the concept of CFs was introduced for the first time in the OMERACT process in a preliminary version of the OMERACT handbook. CFs were defined as: “*variables that are not outcomes of studies, but need to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers*”(9). Several OMERACT-WGs (Worker Productivity(10), Hand-Osteoarthritis(11), Vasculitis(12), RA-Flare(13) and Health Literacy WG(14)), in consideration of input from patient research partners (PRPs), started to include CFs in their research. However, the research presented in OMERACT 2014 revealed great heterogeneity in understanding, approaching and identifying CFs. To address this confusion the CFMG was formed, representing *“an entirely new work stream to address newly identified challenges” (15).* The mission of this group seeks to provide guidance to the OMERACT community and other researchers on the fundamental steps that should be implemented to identify CFs that are essential for interpreting results in the setting of a randomized clinical trial (RCT) in rheumatology. The group consists of clinicians, statisticians, researchers and PRPs from the OMERACT WGs already involved in CF-research. The first objectives of the CFMG were

To agree on the operational definition of CFs (that can be applied to core sets or specific outcomes) among all stakeholders.

To inform the CFMG research agenda on how:

To identify methods for the selection of relevant CFs and for the statistical testing of its impact.

To understand whether the agreed definition can be applied to all settings (core sets, specific outcomes).

In its 2016 report, the CFMG highlighted the need to clarify the concept of “CF” in light of outcome measure development according to the OMERACT process. Based on the OMERACT CF-definition and the International Classification of Functioning, Disability and Health (ICF) framework(16) an operational definition of CFs was agreed on and a research agenda was formulated.

**METHODS**

In spring 2015 the CFMG explored the conceptualization of CFs and previous research by OMERACT WGs engaged in CF research in an email-survey. Ten questions were formulated by the CFMG members addressing the CF definitions used and the approaches to identify potentially important CFs as well as strategies applied to measure and analyze the impact of CFs. (See Table1) The results were tabulated, and the content summarized*.*

At the OMERACT 2016 CFMG-Special Interest Group (SIG) session a preliminary consensus among stakeholders and WGs on a potential operational definition of CFs was established based on an informed discussion. A preliminary list of candidate CFs to be considered when interpreting an outcome in rheumatology clinical trials was collected in a group exercise and on individual written forms (post-SIG questionnaire). Then, the CFMG requested from the SIG-participants recommendations to further develop the research agenda.

**RESULTS**

*Survey of OMERACT WGs*

Response to the survey was received from 8/10 OMERACT WGs: Ankylosing Spondylitis, Equity, Hand-OA, Health Literacy , RA-Flare , Shared Decision-Making , Vasculitis, and Worker Productivity. The survey results are presented in **Table 1** and Appendix1.

Five of the eight groups used the OMERACT handbook 2.0 definition(9), of which three groups also used the CF definition of the ICF, i.e. environmental and personal factors(16). The Health Literacy group defined CF specifically as “a factor / variable that may modify the level or importance of the PRO measured.”

Depending on the specific research focus, multiple methods were used to identify, refine and categorize CF candidate categories including literature search, ICF or ICF core sets(17), expert discussions, patient interview and focus groups, PRP and SIG-participant discussions. This variety emphasized the great heterogeneity in approaching and identifying CFs across OMERACT-WGs.

In their research some WGs identified potential confounders or covariates specific to their research topic, e.g. “patient’s ability to accurately complete a PRO” identified by the Equity group. As another example, self-management was identified initially as a domain to be measured by the RA-Flare WG, but when scoring was explored, variability of answers to questions designed to assess self-management resulted in determining that self-management is probably an effect modifier itself. The ASAS-Health-Index identified nine items of potentially relevant CFs for testing in their new instrument, while others proposed factors used to identify phenotypical subgroups (Hand OA)(18).

*Patient Research Partners*

PRPs initially focused on the influence of CFs on transferability of study results to daily life. However, in discussions PRPs agreed to focus on CF’s influence on the interpretation of outcomes in RCTs (not clinical care or daily life).

*OMERACT-SIG 2016*

Forty-eight participants attended the CFMG SIG session, including 35 HCPs, six fellows, five PRPs, two industry representatives.

After presenting the survey results to the participants, twenty-eight variables were collected verbally and displayed, stimulating active discussion on the operational use of the OMERACT CF definition, the ICF framework, methods to identify CFs and approaches to select core CFs. SIG-participants acknowledged that research is complicated by the large number of CFs. And depending on the setting, the study design, or research question, CFs could be seen either as potential confounders, effect modifiers, (co)-outcomes or even as interventions. These findings were confirmed by thirty-nine participants who provided written input to a post-SIG questionnaire (see appendix 2), of which eleven listed the variables as potential core CFs (**Table 2**).

Moreover the CFMG-SIG-participants agreed that the OMERACT definition (focusing on effect modification in most settings) should be used as the main operational definition with the ICF as the conceptual framework. They confirmed the relevance of the CFMG as an OMERACT methods group to provide guidance to other groups in identifying, measuring, and characterizing important/core CFs.

Furthermore, the CFMG SIG-participants made the following recommendations for the research agenda

* The CFMG should closely collaborate with other WGs, as these groups may develop measures for CFs.
* Statistical methods are needed to prove the impact of CFs on effect modification. As a first step identifying existing data sets that can be used for secondary analysis should be considered.

Based on these recommendations the CFMG formulated three main projects as first steps to provide guidance to identify and characterize CFs that significantly influence the interpretation of results in CTs:

a) Delphi exercises (including experts and patients) to identify CFs of importance within rheumatology with suspected effect modification.

b) Literature reviews to find evidence whether these CFs are affecting the effect sizes in either RCTs (using stratification or post-hoc analyses) or in meta-analyses, and (19)

c) Exploration of how a CF should be (validly) measured.

**Discussion and Conclusions**

In the context of outcome measurement in Rheumatologic CTs the OMERACT Handbook definition of CFs, focusing on effect modification and using the ICF as conceptual framework was found to be pertinent. Although it is important to note that this definition depicts CFs that are relevant to interpret outcomes of clinical trials and may not cover the needs of clinical practice settings (20-22).

Despite the consensus on an CF definition, the characterization of core CFs remains a challenge, partially because the influence of most CFs tends to vary according to the context(23). A great number of CFs have been identified as potentially relevant in interpreting outcomes of RCTs, although only a few might fulfil the definition of effect modification(24).

As healthcare evolves toward person-centered medicine, CFs might be key to optimize treatment allocation. However, to even have the opportunity to prove the effect of a distinct CF, studies providing strong arguments for including that specific CF in RCTs are first needed(19, 25-27) and will provide a next step in understanding the impact of CFs on outcomes in CT.

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