Collecting examples of contextual factors that have an impact on the trial outcome: A concise protocol for a survey of OMERACT working groups

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ABSTRACT

Introduction: In 2012, the concept of contextual factors (CF) was introduced for the first time in the OMERACT process, but understanding, approaching, and identifying CF proved difficult. The Contextual Factors Working Group (CFWG) was formed to provide guidance on how to address these challenges of CFs in clinical trials. In the CFWG there is consensus that, initially, relevant examples of case scenarios are needed.

Objectives: The primary objective of this study is to collect examples of case scenarios (in a trial setting) involving contextual factors that have an important impact on the trial outcome from all OMERACT working groups.

Methods and analysis: In this study, we will utilize an e-mail based survey of OMERACT working groups, and subsequently review the answers in order to select a few case scenarios particularly relevant for future studies within the CFWG.

Dissemination: The results of this study will be reported as part of future studies from the CFWG and will primarily be presented in appendixes.

Perspectives: The results from this study will work as a primer for future studies within the work by the CFWG, which aims at providing guidance on how to address CFs in future clinical trials.

INTRODUCTION

A core outcome (measurement) set is a minimum consensus-based set of outcome domains and instruments that should be measured and reported in all clinical trials for a specific health condition and/or intervention. Since 1992, the Outcome Measures in Rheumatology (OMERACT) consensus initiative has successfully developed core sets for many rheumatologic conditions, actively involving patients since 2002 [1]. As other initiatives, like the Core Outcome Measures in Effectiveness Trials (COMET) started to formalise the existing methodology, OMERACT's expanding scope required an explicit formulation of its underlying conceptual framework and process [1].

According to the current principles, core set developers need to specify the setting of the core set, and consider if there are any contextual factors (CF) that need to be measured in the trials. In 2012, the concept of CF was introduced for the first time in the OMERACT process in a preliminary version of the OMERACT Handbook. However, the research presented in OMERACT 2014 revealed great heterogeneity in understanding, approaching, and identifying CF [2]. To address this, the Contextual Factors Working Group (CFWG) was formed with the objective to provide guidance on how to address CFs in clinical trials. At the OMERACT 2016 CFWG SIG session, the participants agreed that the OMERACT Handbook definition should be used as the main operational definition and the definition by the International Classification of Functioning, Disability and Health (ICF) should be used as the conceptual framework [3]. In the current version of the OMERACT Handbook, CF is defined as a "*variable that is not an outcome of the study, but needs to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers*" [4]. This definition is rather simple and lacks important details for being applicable, hence, it currently hampers the consideration of CF in future research.

Within the ICF framework of functioning and health, contextual factors are defined and further divided into environmental factors and personal factors; "*Environmental factors make up the physical, social, and attitudinal environment in which people live and conduct their lives. Personal factors are the particular background of an individual's life and living, and consist of features of the individual that are not part of a health condition or health states.*" [5].

At the OMERACT 2016 CFWG SIG session, however, it was discussed that contextual factors in trials could also be related to health condition (such as disease duration) and study

characteristics (such multicenter vs single-center trials), and hence not necessarily covered by the ICF. However, in the CFWG there is consensus that, initially, relevant examples of case scenarios, demonstrating specific contextual factors that affect trial outcomes, are needed as a first step in the process, and will work as a primer for future studies within the group.

Objectives

The primary objective of this survey is to collect examples of case scenarios (trial settings) involving contextual factors with an important impact on the trial outcome from all OMERACT working groups.

METHODS

Protocol

This concise protocol will be published online on the Parker Institute web page (www.parkerinst.dk) prior to conducting the survey.

Study design

In this study, we will utilize an e-mail based survey of OMERACT working groups, and subsequently review the answers in order to select a few case scenarios particularly relevant for future studies within the CFWG.

Participants and setting

The participants will be members of all active OMERACT working groups (**Table 1**, except the CFWG); these will be contacted via the chairs of each WG.

Table 1: **Active OMERACT working groups**

- **ANCA Vasculitis (Core Set)**
- **AS-Reference Case**
- **Behçet's Syndrome**
- **CTD-ILD**
- **Fibromyalgia (Core Set)**
- **Flares in OA**
- **Flares in RA**
- **Glucocorticoid Adverse Events**
- **Gout**
- **Hand OA**
- **ICF**
- **JIA Core Set**
- **Large Vessel Vasculitis**
- **Myositis**
- **Osteoarthritis (Core Set)**
- **Osteoporosis (Core Set)**
- **Pain**
- **Polymyalgia Rheumatica (PMR)**
- **Psoriatic Arthritis**
- **Remission in RA-patient perspective**
- **Rheumatoid Arthritis (Core Set)**
- **Shoulder Pain Outcome Measures**
- **Systemic Lupus Erythematosus**
- **Total Joint Replacement**
- **Gout Biomarker Group**
- **MRI in Arthritis**
- **JAMRI**
- **Soluble Biomarkers**
- **SPECTRA**
- **Synovial Tissues in RCT**
- **Ultrasound**
- **CAT & IRT**
- **Consensus for Consensus**
- **Critical Outcomes in Longitudinal Studies**
- **Safety in Rheumatology Clinical Trials Working Group**
- **Equity**
- **QALYs**
- **RASCH and MID**
- **Health Literacy**
- **Medication Adherence**
- **Shared Decision Making**
- **Stiffness**
- **Worker Productivity**

The chairs of the working groups will receive a short email with an attached document including instructions, illustrative examples and the survey form (**Appendix 1**). If no response is received after the deadline, two reminders will be sent out two and seven days after the deadline, respectively.

Data processing

From the completed forms, duplicate answers (i.e. the same case scenario provided by several working groups) will be compared and interpreted based on a PICOCT-framework (population, intervention, comparison, outcome, contextual factor, time). All publications, referred to in the feedback, will be retrieved. The answers will be reviewed for any erroneous entries by one researcher (SMN) supported by another researcher (RC), and, if needed, mails may be sent with clarifying questions to the respective co-chairs of the working group. If any case scenario is deemed invalid by both researchers (SMN and RC), they will be excluded. All valid case scenarios will be presented in a table in a uniform manner. From this table, at least three case scenarios will be selected based on:

- **The disease involved**; preferably, all three case scenarios should involve different diseases
- **The type of contextual factors involved**; at least one example should involve environmental contextual factors
- **Method of handling contextual factors**; a variety in methods between the case scenarios will be aimed for
- **General value for future studies within the CFWG** (i.e. especially an upcoming study using semi-structured interviews of experts)

Preference will be given though, to potentially core contextual factors if more than one working group indicate that this generic construct applies across multiple conditions/interventions (e.g. sex, age, and comorbidities).

PERSPECTIVES AND DISSIMINATION

The results from this study will work as a primer for future studies within the work by the CFWG, which aims at providing guidance on how to address CFs in in future clinical trials. The results of this study will be reported as part of future studies from the CFWG and will primarily be presented in appendixes.

Acknowledgments

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APPENDIX 1: Instructions, illustrative example and the survey form

Dear OMERACT working group

We need your participation in this survey regarding contextual factors, since it will facilitate our work in defining contextual factors.

What is a contextual factor?

Contextual factors are not clearly defined (yet), however, according to the current version of the OMERACT Handbook, a contextual factor is defined as a:

> *"variable that is not an outcome of the study, but needs to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers"* **Boers M, Kirwan JR, Tugwell P, et al. The OMERACT Handbook**

Please also take into account the International Classification of Functioning, Disability and Health (ICF) definition of a contextual factor, which they divide into environmental factors and personal factors (*note, however, that the ICF is concerned with a health model framework, whereas OMERACT is concerned with an outcome framework*):

> *"Environmental factors make up the physical, social, and attitudinal environment in which people live and conduct their lives. Personal factors are the particular background of an individual's life and living, and consist of features of the individual that are not part of a health condition or health states."* **WHO: International classification of functioning, disability and health: ICF. Geneva: WHO, 2001**

What do you have to do in this survey?

We would like you to provide at least one example/case scenario (trial settings), which is relevant for your field of research, and where contextual factors are strongly suspected to (or even proven to) have an impact on clinical trial results (i.e. net benefit).

Please, follow these guidelines:

- The scenario(s) need to take basis in trials
- The scenario(s) should preferably be published (e.g. it may be based on a trial report or meta-epidemiological study)
- When answering, you should provide scenario(s) that includes both types of contextual factors (i.e. personal and environmental), if possible
- Include, preferably, inputs from at least one patient and at least one clinician in your answers

Please return the filled out survey form within three weeks, i.e. before the [DATE INSERTED HERE].

Thank you very much for your help.

On behalf of the OMERACT Contextual Factor Working Group (CFWG)
Robin Christensen *(CFWG co-chair),* ***Christoph Pohl*** *(CFWG co-chair), and* ***Sabrina Mai Nielsen*** *(CFWG fellow)*

Working Group: RA Remission WG / PSA WG **ILLUSTRATIVE EXAMPLES**

CASE SCENARIO 1

Population: Rheumatoid Arthritis
Intervention: Targeted therapies (biologics)
Outcome: ACR20
Personal contextual factor(s): DMARD-history
Environmental contextual factor(s): -
Explanation: This study is a meta-epidemiological study. Findings include: Net benefit is 2.2 times better in DMARD-IR than DMARD-Naive Pts (OR: 4.34 vs 1.97)
Publication (if applicable): Christensen AW et al. (PLoS One, 2015)

CASE SCENARIO 2

Population: Patients with psoriatic disease
Intervention: Any targeted therapies approved for psoriatic arthritis and psoriasis
Outcome: ACR20
Personal contextual factor(s): Prior therapy, disease duration, rheumatoid factor and CASPAR criteria
Environmental contextual factor(s): -
Explanation: This study is a meta-epidemiological study. Quote: The eligibility criteria “targeted therapy history”, “minimum required disease duration”, “required negative rheumatoid factor”, and “required CASPAR criteria” were of importance for achieving ACR20 in PsA.
Publication (if applicable): Ballegaard C et al. (Arthritis Care Res (Hoboken). 2017)

Working Group: Write your answer here

CASE SCENARIO 1

Population: Write your answer here
Intervention:Write your answer here
Outcome: Write your answer here
Personal contextual factor(s): Write your answer here
Environmental contextual factor(s): Write your answer here
Explanation: Write your answer here
Publication (if applicable): Write your answer here

CASE SCENARIO 2

Population: Write your answer here
Intervention: Write your answer here
Outcome: Write your answer here
Personal contextual factor(s): Write your answer here
Environmental contextual factor(s): Write your answer here
Explanation: Write your answer here
Publication (if applicable): Write your answer here

CASE SCENARIO 3

Population: Write your answer here
Intervention: Write your answer here
Outcome: Write your answer here
Personal contextual factor(s): Write your answer here
Environmental contextual factor(s): Write your answer here
Explanation: Write your answer here
Publication (if applicable): Write your answer here
Population: Write your answer here

EXTRA (OPTIONAL)

The next upcoming study within the CFWG aims at providing a **clear and elaborated (operationalised) definition of contextual factors.** This will be done through **semi-structured interviews of experts** (incl. statisticians, methodologists, and trialists) who may be considered experts within a contextual factor (or potentially similar subjects such as predictive/prognostic factors, effect modifiers, subgroup effects, or stratified analyses/interaction) related field.

If you have any specific and/or general issues regarding contextual factors from your working group, which you recommend us to get addressed in the interviews, fell free to state them below (*e.g. definition, related terminology, classification, handling of contextual factors in planning and analysis of trials etc.*):

Regarding contextual factors, we recommend that the experts address the following issue(s): Write your answer here