Journal Pre-proof

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PII: S0049-0172(21)00044-5
DOI: https://doi.org/10.1016/j.semarthrit.2021.03.013
Reference: YSARH 51814

To appear in: *Seminars in Arthritis & Rheumatism*

Please cite this article as: Sabrina Mai Nielsen , Maarten Boers , Maarten de Wit , Beverly Shea , Danielle A. van der Windt , Barnaby C. Reeves , Dorcas Beaton , Rieke Alten , Karine Toupin April , Annelies Boonen , Reuben Escorpizo , Caroline Flurey , Daniel E. Furst , Francis Guillemin , Amye Leong , Christoph Pohl , Marianne Uggen Rasmussen , Jasvinder A. Singh , Josef S. Smolen , Vibeke Strand , Suzanne M.M. Verstappen , Marieke Voshaar , Thasia G. Woodworth , Torkell Ellingsen , Lyn March , George A. Wells , Peter Tugwell , Robin Christensen , OMERACT consensus-based operational definition of contextual factors in rheumatology clinical trials: a mixed methods study, *Seminars in Arthritis & Rheumatism* (2021), doi: https://doi.org/10.1016/j.semarthrit.2021.03.013

OMERACT consensus-based operational definition of contextual factors in rheumatology clinical trials: a mixed methods study

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Word count: **1493**; Tables and figures: **3**; References: **14**; Appendix: **0;** Online data supplements: **10.**

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ABSTRACT

Objectives: To develop an operational definition of contextual factors (CF) [1].

Methods: Based on previously conducted interviews, we presented three CF types in a Delphi survey; Effect Modifying -, Outcome Influencing - and Measurement Affecting CFs. Subsequently, a virtual Special Interest Group (SIG) session was held for in depth discussion of Effect Modifying CFs.

Results: Of 161 Delphi participants, 129 (80%) completed both rounds. After two rounds, we reached consensus (≥70% agreeing) for all but two statements. The 45 SIG participants were broadly supportive.

Conclusion: Through consensus we developed an operational definition of CFs, which was well received by OMERACT members.

Keyword: OMERACT, Contextual Factors, Delphi survey, Effect Modifying Contextual Factors, Outcome Explaining Contextual Factors, Measurement Affecting Contextual Factors

INTRODUCTION

The Outcome Measures in Rheumatology (OMERACT) initiative [1] established the Contextual Factors Working Group to guide the understanding, identification and handling of contextual factors (CFs) in clinical trials [2, 3] (https://omeract.org/working-groups/contextual-factors/). Initially, OMERACT defined a CF 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].

The working group explored patient, clinician and researcher perspectives in semi-structured interviews [5] and identified four types of CFs describing different ways that CFs can influence trial results. These CF types were initially termed Effect Modifying (EM-CFs), Meta Confounding (MC-CFs), Measurement Affecting (MA-CFs) and Outcome Explaining (OE-CFs). Of these, three are relevant for individual clinical trials (i.e. EM-CFs, MA-CFs, OE-CFs) and, hence, OMERACT [5].

In this study, we aimed to develop a consensus-based operational definition of CFs, that is a definition that can be used to guide the understanding, identification and handling of CFs in individual clinical trials within rheumatology.

Methods

This study represents the two final stages of a mixed methods study consisting of i) semi-structured interviews [5], ii) an iterative consensus Delphi survey and iii) a virtual Special Interest Group (SIG) session for discussion.

For the Delphi, we followed a predefined protocol, based on relevant guidelines [6-8]. The study was carried out in accordance with the Helsinki Declaration and approved by the Danish Data Protection Agency (ID 06081, BFH-2017-127).

We developed the Delphi survey based on findings from our semi-structured interviews [5]. We invited all 974 listed members of the OMERACT community (including 85 patient research partners) to participate in the online Delphi survey. The survey included a section for each of the three CF types (EM-CFs, OI-CFs and EM-CFs) and an overarching section addressing general issues. Each section was introduced with a description including a case scenario, followed by statements to be rated on a Likert numeric rating scale from 1 to 9 (1-3, Disagree; 4-6, Undecided; 7-9, Agree), with the option 'Unable to score' and to provide comments. Agreement by stakeholders (i.e. patients and clinicians/others) required ≥70% scoring 7 to 9 and disagreement required ≥70% scoring 1 to 3 [6]. Consensus was achieved if both stakeholder groups agreed (or disagreed) with the statement.

We conducted two survey rounds in 2020, from March 2nd to April 6th and June 15th to July 23rd respectively. Everyone who signed up as participant were invited for both rounds, whether or not they completed the first round. Between rounds, the steering group discussed the results and feedback and agreed on modifications of the descriptions and statements. The participants were informed about modifications and their previous ratings (if any) before initiating the next round. We used DelphiManager software (www.comet-initiative.org/delphimanager/), that ensures confidentiality. Participants could offer consent if they agreed to being contacted regarding comments needing further clarifications. We analysed data using R (version 4.0.1) [9]. See protocol and protocol deviations for further details on methods (supplemental material).

We conducted a 1-hour virtual SIG session on November 12th as part of the virtual OMERACT 2020 meeting, for which the OMERACT secretary invited all OMERACT members and others interested via email and social media (Facebook, Twitter and LinkedIn). We developed preparatory material based on the Delphi results, including two videos, a quiz, a lay summary, a glossary list and a pre-reading text. Further, we asked participants to provide published examples of EM-CFs in advance. The session focussed on EM-CFs due to previous progress and limited time. During the session, we presented EM-CFs in further detail, allowing for further discussion and understanding of the concept of EM-CFs.

Results

A total of 161 individuals signed up for our Delphi survey (Figure 1), including 33 (20%) patients and 128 (80%) clinicians/others. Of these, 29 (88%) patients and 100 (78%) clinicians/others completed both survey rounds fully.

[Figure 1 approximately here]

The patients signing up for the Delphi were 24 (73%) females, mean age was 57.1 (SD, 11.1) and represented a wide range of rheumatic conditions, but mostly rheumatoid arthritis (30%), psoriatic arthritis (21%) and osteoarthritis (12%). Clinicians/others signing up were 71 (55%) females, mean age was 51.3 (SD, 11.9) and 80 (63%) were involved in rheumatology patient care. Forty-three (out of 44 active) OMERACT working groups and 26 countries from five continents, but mostly North America and Europe, were represented (see all characteristics in supplemental material).

In round 1, consensus was achieved for 19 out of 28 statements (68%). The participants provided 394 comments on the statements, 38 general comments and 11 suggestions for additional statements. Statements with no consensus were mainly related to OE-CFs and many participants expressed

difficulty distinguishing between the CF types. This guided the modifications for round 2. 'Outcome Explaining' CFs were now called 'Outcome Influencing' CFs (OI-CFs) and the description was rewritten. For round 2, 14 statements with consensus were removed, some were reformulated and 6 new statements were added.

In round 2, consensus was achieved for 18 out of 20 statements (90%), with 36 general comments. Lack of consensus was related to classification categories for the MA-CFs (see details in supplemental material). The steering group deemed the two statements less important and conducting a third survey round was not necessary. Two important overarching statements, which reached consensus, were *´I consider the three types of contextual factors to adequately cover the concept contextual factors'* (97% and 92% patients and clinicians/others agreeing, respectively) and *´I can distinguish between the three different types of contextual factors'* (93% and 86% agreeing) (see survey results in supplemental material).

Based on the survey results, we finalized the operationalized definition of CFs (Figure 2) and presented it as part of the preparatory material for the SIG session (see supplemental material).

[Figure 2 approximately here]

Forty-five individuals attended our virtual SIG (Figure 1); 14 (31%) patients, 30 (67%) clinicians/researchers and 1 (2%) regulator, representing 17 countries from 4 continents. Thirty-four (76%) had participated in our Delphi survey. Of our preparatory material, the two videos were the most popular, and only 2 (5%) had not used any material (Figure 3). In advance, 8 SIG participants (2 patients and 6 clinicians/researchers) had provided examples of EM-CFs for the session. Three examples were selected and presented [10-12].

The SIG participants were actively engaged in the Q&A session and discussions, and statistical questions were frequent. It was emphasized that trial reports should present treatment effects separately for subgroups according to EM-CFs (e.g. in their appendix), to make these available for future meta-analyses. P-values for interaction tests are generally being phased out due to risk of type-II errors.

Distinguishing EM-CFs from OI-CFs was mentioned as a challenge, but one suggested that OI-CFs relates to the disease progression, while EM-CFs relates to the treatment effect. Some were concerned that EM-CFs may depend on the intervention, but it was clarified that we will initially look for factors frequently shown and/or strongly suspected to be EM-CFs across different interventions. The OMERACT working groups should not be responsible for providing such evidence, when identifying EM-CF for their core sets, but simply note where more research is needed.

The poll indicated that most SIG participants understood the concept of EM-CFs 'very well' and found the criteria 'very helpful' (Figure 3). After the session, the recording was made available online (available from the corresponding author).

[Figure 3 approximately here]

Discussion

In this study, we achieved consensus on an operational definition of CFs including three types (i.e. EM-CFs, MA-CFs and OI-CFs) and introduced it to the OMERACT community. We believe this definition will help to resolve most of the confusion related to CFs, as our elaboration of the initial OMERACT definition embraces different views on CFs.

Our work is likely relevant across most OMERACT working groups. EM-CFs are relevant for all groups developing core outcome sets for clinical trials. OI-CFs relates to non-randomized trials and may be relevant for groups such as the Patient Outcomes in Longitudinal Observational Studies (POLOS) group [*ref to their OMERACT 2020 publication if possible*] and work productivity [13]. MA-CFs are relevant for all groups developing core outcome measurement sets [14]. Some groups work with concepts related to MA-CFs, such as the equity extension for the OMERACT instrument selection process [*ref to their OMERACT 2020 publication if possible*] and sources of variability for outcome measurement instruments by the Imaging group [*ref to their OMERACT 2020 publication if possible*].

Consideration of CFs has the potential to improve the measurement of outcomes (i.e. MA-CFs), interpretation of non-randomized trials and identification of patients with poor prognosis (i.e. OI-CFs), and improving treatment of patients (i.e. EM-CFs). Strengths of our work include the large number and international representation of the participants. Active engagement led to many comments from different perspectives, which guided the modifications of our definition. However, the material was only provided in English, and individuals from Africa, Asia and South America were under-represented. We consider our definition to be provisional, allowing for future adjustments if necessary.

In conclusion, we have developed and achieved OMERACT agreement on an operational definition of CFs. We anticipate this definition will improve understanding, identification and handling of CFs when developing core outcome sets within OMERACT, as well as facilitate research on CFs generally in rheumatology.

Author contributions

Amye Leong: Conceptualization, Writing - Review & Editing; **Annelies Boonen**: Conceptualization, Resources, Writing - Review & Editing; **Barney Reeves**: Conceptualization, Methodology, Validation, Writing - Review & Editing; **Beverley Shea**: Conceptualization, Methodology, Writing - Review & Editing, Supervision; **Caroline Flurey**: Conceptualization, Methodology, Writing - Review & Editing; **Christoph Pohl**: Conceptualization, Writing - Review & Editing, Supervision; **Daniel E Furst**: Conceptualization, Validation, Writing - Review & Editing; **Danielle van der Windt**: Conceptualization, Methodology, Writing - Review & Editing; **Dorcas Beaton**: Conceptualization, Methodology, Writing - Review & Editing, Supervision; **Francis Guillemin**: Conceptualization, Writing - Review & Editing; **George A Wells**: Conceptualization, Methodology, Validation, Writing - Review & Editing, Supervision; **Jasvinder Singh**: Conceptualization, Writing - Review & Editing; **Josef Smolen**: Conceptualization, Methodology, Writing - Review & Editing; **Karine Toupin-April**: Conceptualization, Writing - Review & Editing; **Lyn March**: Conceptualization, Methodology, Writing - Review & Editing, Supervision; **Maarten Boers**: Conceptualization, Methodology, Validation, Writing - Review & Editing; **Maarten de Wit**: Conceptualization, Methodology, Investigation, Writing - Review & Editing; **Marianne Uggen Rasmussen**: Conceptualization, Methodology, Writing - Review & Editing, Supervision; **Marieke Voshaar**: Conceptualization, Writing - Review & Editing; **Peter Tugwell**: Conceptualization, Methodology, Writing - Review & Editing, Supervision; **Rieke Alten**: Conceptualization, Writing - Review & Editing; **Reuben Escorpizo**: Conceptualization, Validation, Writing - Review & Editing; **Robin Christensen**: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Funding acquisition; **Sabrina Mai Nielsen**: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration Funding acquisition; **Suzanne Verstappen**: Conceptualization, Validation, Writing - Review & Editing; **Thasia G Woodworth**: Conceptualization, Writing - Review & Editing; **Torkell Ellingsen**: Conceptualization, Writing - Review & Editing, Supervision, Funding acquisition; **Vibeke Strand**: Conceptualization, Methodology, Writing - Review & Editing.

Declaration of Competing Interest

Dr. Alten reports personal fees from Abbvie, personal fees from BMS, personal fees from Celltrion, grants from Galapagos, personal fees from Gilead, personal fees from Lilly, grants and personal fees from Pfizer, outside the submitted work. **Annelies Boonen** received research grants form Celgene and Abbvie and fees for advisory boards from Abbvie, Eli Lilly and Galapagos, all paid to her department. **Dr. Furst** reports NO stocks, royalties, direct financial holding, expert testimony, board of director. Grant/Research Support Actelion, Amgen, BMS Corbus, Galapagos GSK, NIH, Novartis, Pfizer, Sanofi, Roche/Genentech. Consultant

Actelion, Amgen, BMS, Corbus, Galapagos Novartis, Pfizer, Speakers Bureau CME only. **Dr. March** reports personal fees from Pfizer Australia Ltd, personal fees from Bristol Myer Squibb Australia, personal fees from Elsevier Ltd, personal fees from Up To Date, grants from Janssen Australia, outside the submitted work; and LM is a member of the executive of OMERACT. **Dr. Shea** reports being the senior methodologist on this project. **Dr. Singh** reports personal fees from Crealta/Horizon, Medisys, Fidia, UBM LLC, Trio health, Adept Field solutions, Medscape, WebMD, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigant consulting, Spherix, Practice Point communications, the National Institutes of Health and the American College of Rheumatology, personal fees from Simply Speaking, other from Amarin, Viking, Moderna and Vaxart pharmaceuticals; and Charlotte's Web Holdings, non-financial support from FDA Arthritis Advisory Committee, non-financial support from Steering committee of OMERACT, non-financial support from Veterans Affairs Rheumatology Field Advisory Committee, non-financial support from Editor and the Director of the UAB Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis, outside the submitted work. **Dr. Smolen** received grants to his institution from Abbvie, AstraZeneca, Janssen, Lilly, Merck Sharpe & Dohme, Pfizer, and Roche and provided expert advice for, or had symposia speaking engagements with, AbbVie, Amgen, AstraZeneca, Astro, Bristol-Myers Squibb, Celgene, Celltrion, Chugai, Gilead, ILTOO Pharma, Janssen, Lilly, Merck Sharp & Dohme, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi, and UCB. **V. Strand** is a member of the executive of OMERACT. **OMERACT**, an organization that develops outcome measures in rheumatology, receives arms-length funding from 8 companies. **The other authors** have no conflict of interest relevant to the content of this study.

Funding

The Parker Institute is grateful for the financial support received from public and private foundations, companies, and private individuals over the years. The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL); The Oak Foundation is a group of philanthropic organisations that, since its establishment in 1983, has given grants to not-for-profit organisations around the world. SMN has received PhD Scholarships from the Faculty of Health Sciences, University of Southern Denmark, and Odense University Hospital, and an introductory scholarship from the BFH Research Foundation. Furthermore, The Danish Rheumatism Association covered costs related to the fees of the OMERACT meeting. The funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data of the study and had final responsibility for the decision to submit for publication.

Acknowledgements

We would like to thank the pilot testers, including the patient research partners, Catherine Hofstetter, Mary Cowern, and Thomas Buttel, and the clinicians/researchers, Margreet Kloppenburg, Sofia Ramiro, Richard Holland, Ayano Kelly, Peter Wong. The feedback from the pilot tests has played an important role in shaping the final version of the survey.

We would like to thank all who participated in our Delphi survey. In particular, we would like to thank those completing both Delphi rounds including (but not limited to): Dr. Allyson Jones, Dr. Ana-Maria ORBAI, Dr. Andrea Delle Sedie, Ms. Anne Boel, Emeritus Professor Anne E Ashford, Doctor Anne-Priscille Trouvin, Dr. Antonio Manzo, Mr. Ben Horgan, Ms. Catherine Hofstetter, Dr. Cèsar Díaz-Torné, Emeritus Professor Charles H Goldsmith, Mr. CHAU Sze Ngai Jeffrey, Professor Désirée van der Heijde, Professor Dirkjan van Schaardenburg, Professor Ernest Choy, Ms. Esen Cam, Dr. Féline Kroon, Professor Francesca Ingegnoli, Professor Francis Berenbaum, Ms. Georgia Lanier, Ms. Gerd Jenny Aanerud, Mrs Heidi Nugent, Program Director Heiyoung Park, Dr. Hemalatha Srinivasalu, Ms. Ingrid de Groot, Professor J.A.P. da Silva, Dr. James R. Seibold, Dr. Kaitlin A. Quinn, Dr. Kathleen Tymms, Professor Leigh F Callahan, Professor Lene Terslev, Dr. Loreto Carmona, Mrs. Lorna Neill , Professor Margreet Kloppenburg, Professor Marian T. Hannan, Dr. Maria A. Lopez-Olivo, Dr. Marion A.J. van Rossum, Dr. Marion C. Kortekaas, Ms. Mary Cowern, Dr. Matthew Page, Professor Merete Lund Hetland, Associate professor Mihir D Wechalekar, Mr. Michael Gill, Dr. Mike Backhouse, Dr. Mitali Sen, Dr. Monique A. M. Gignac, Professor Nicola Dalbeth, Dr. Niti Goel, Dr. Owen Hensey, Professor Peter A. Merkel, Dr. Polina Putrik, Professor Randall M. Stevens, Assistant Professor Raouf Hajji, Dr. Ricardo J. O. Ferreira., Dr. Richard Veselý, Professor Dr. Ruth Wittoek, Dr. Sara Tedeschi, Dr. Serena Carville, Ms. Shannon E. Kelly, Ms. Sharon Lee, Dr. Simon Otter, Dr. Sofia Ramiro, Professor Dr. Sule Yavuz, Professor Susan Bartlett, Professor Susanna Proudman, Dr. Tarimobo Michael Otobo, Mr. Thomas W Buttel, Dr. Tiffany K Gill, Professor Till Uhlig, Dr. Toby Smith, Dr. Ulrike Kaiser, Dr. Victoria Navarro-Compán, Dr. Violeta Vlad, Associate Professor William J. Taylor, Ms. Zabalan Minisoara Codruta, Mr. Zoltan Harsanyi.

We would like to thank Richard Crew for continuous and rapid support for DelphiManager.

We would like to thank all who participated in our virtual SIG session, including (but not limited to) Professor Adewale Adebajo MBE, Ms. Ingrid de Groot, Dr. Mike Backhouse, Dr. Richard Veselý, Dr. Saurab Sharma, Ms. Shannon Kelly, Dr. Sofia Ramiro, Mr Thomas Buttel, Dr. Uta Kiltz, Dr. Win Min Oo.

We would like to give a special thanks to Dr. Francesca Ingegnoli and Dr Mike Backhouse for reviewing the manuscript, improving readability, and to Dr. Saurab Sharma for reviewing the manuscript, improving language and readability.

An enormous thanks to the OMERACT secretary, Shawna Grosskleg, for continuous support, circulating invitations for our SIG meeting, ensuring easy access to our preparatory material through our website, setting up and managing all technical aspects of the Zoom call and much more.

And finally, we would like to thank everyone in our working group not mentioned here. We are thankful for the interest and engagement in our working group and in the concept 'contextual factors'.

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Figure legends

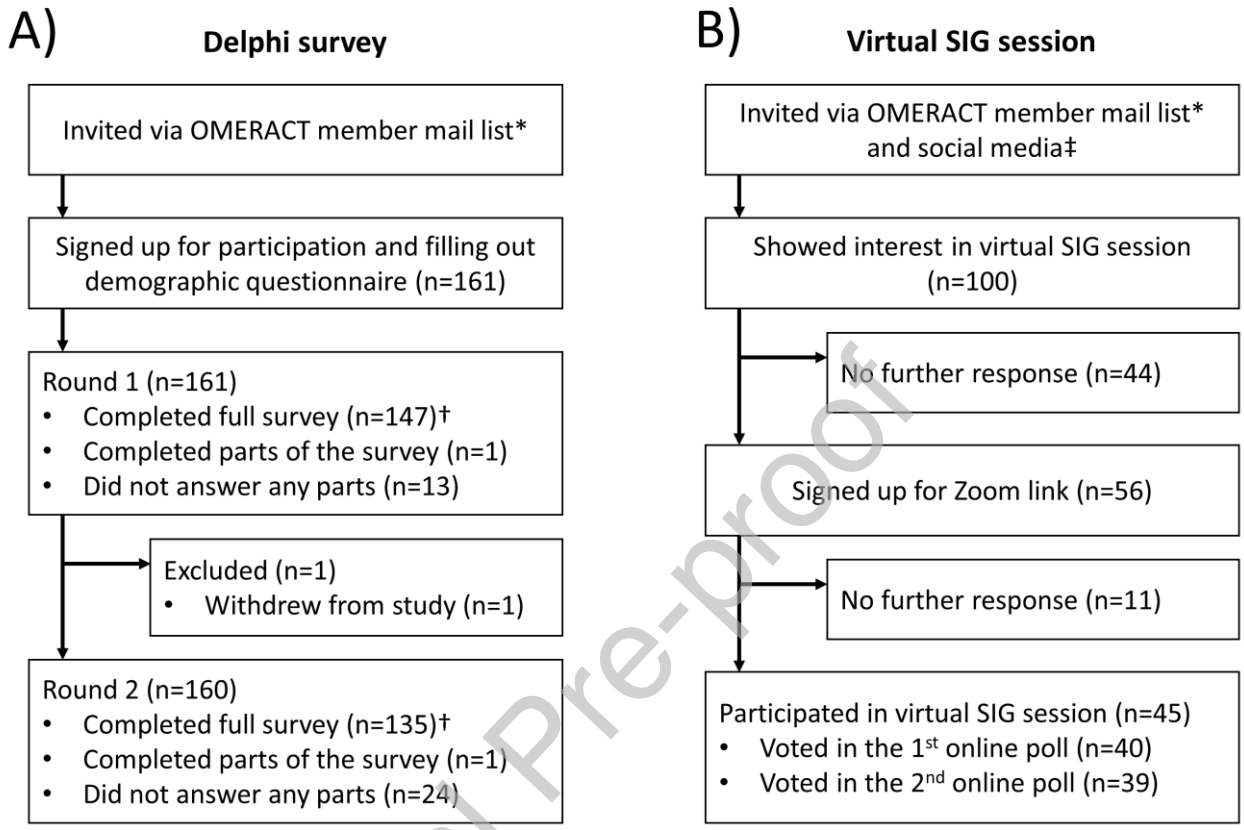

Figure 1: Flow diagram for the Delphi survey (A) and the virtual Special Interest Group session (B)

*The OMERACT member mail list include 974 email addresses, of which 85 are patients. However, it is anticipated that the list includes many that are no longer active OMERACT members, have retired, or for other reasons are not possible to reach through email contact.
†129 completed the full surveys in both rounds
‡ The OMERACT secretary invited potentially interested people outside OMERACT to join the virtual sessions as part of the OMERACT 2020 virtual meeting via social media (i.e. Facebook, Twitter and LinkedIn).
OMERACT, Outcome Measures in Rheumatology; SIG, Special Interest Group.

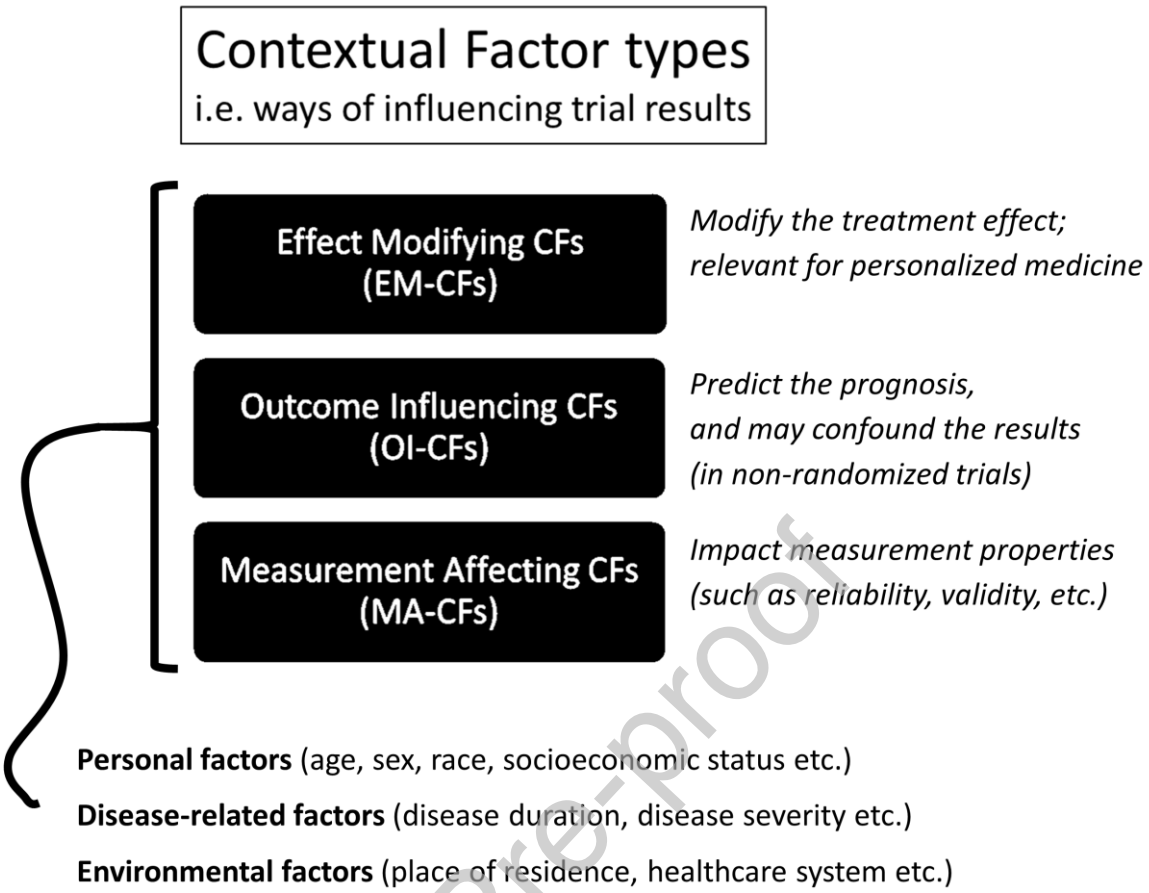

Figure 2: Overview of the consensus-based operational definition of contextual factors

The three contextual factor types describe different ways that contextual factors can influence the results of a trial. Brief descriptions of each type are shown on the figure. All three are described in detail in the supplementary material. To guide which possible factors could be considered within each of these types, specific factors must fit within one of the three classification categories, i.e. either personal-, disease-related, or environmental factors. The contextual factor types are *not* mutually exclusive, so some specific factors may both be an EM-CFs, OI-CFs and MA-CF. In short, EM-CFs modifies the treatment effect (i.e. some patient subgroups experience greater or less effect from a treatment compared to other subgroups). OI-CFs are prognostic factors (sometimes called risk factors), i.e. factors predicting the course of a patient's condition and may confound the results of trials which are not randomized. MA-CFs influences the performance of outcome measurement instruments (such as reliability, validity, responsiveness, etc.).
CFs, Contextual Factors.

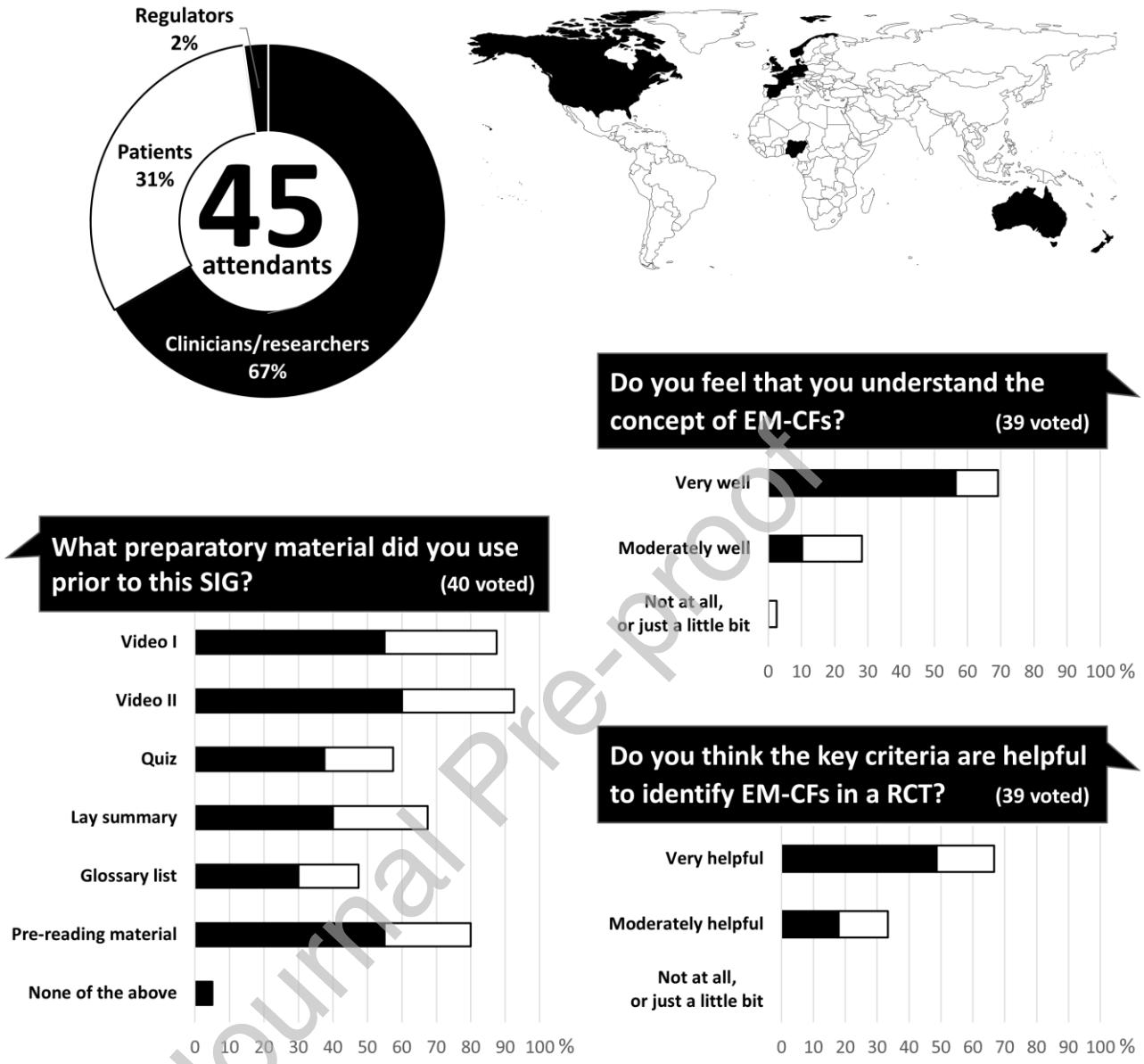

Figure 3: Poll results from virtual Special Interest Group (SIG) session

Distribution of participants according to stakeholder groups and country of residence. Two polls were used during the session. Black indicate clinicians/researchers/others and white indicate patients. The first poll asked participants which preparatory material they had used (left) and it was possible to pick several options. The second poll included two questions (right), asking the participants about their understanding of EM-CFs and whether they considered the key criteria for EM-CFs useful, respectively, and it was only possible to pick one option for each question.
EM-CFs, Effect Modifying Contextual Factors; RCT, Randomized Controlled Trial.