Background Adherence to current monomorbidity-focused, mono-disciplinary guidelines may result in undesirable effects for persons with several comorbidities, in adverse interactions between drugs and diseases, conflicting management strategies, and polypharmacy. As yet no satisfactory approaches exist to address multimorbidity (MM) in clinical guidelines since this patient group is too heterogeneous as to be met by guideline recommendations.

Objectives to develop a set of case-based (N=1) guidelines for common disease combinations identified through epidemiological research and expert (GP) consultations.

Methods We followed a new 5-step, mixed methods approach comprising: (1) review of epidemiological data on MM patterns; (2) interdisciplinary focus groups developed case vignettes according to both internal evidence and the results of step 1; (3) development of case-based recommendations according to case vignettes (N of one guidelines); (4) informal consensus of recommendations; (5) formal consensus.

Results Step one revealed three different approaches for the selection criteria of case vignettes: first, cases addressing MM disease patterns from epidemiological studies (MM clusters); second, cases addressing triads of the 6 most prevalent chronic conditions; third, cases according to a problem-oriented prioritisation of focus group participants. All in all 10 N-of-one guidelines according to 10 cases could be developed according to the new 5-step-process.

Discussion We present a new approach in order to capture the complex and heterogeneous problems of MM through evidence-based and case-based recommendations. This set of N-of-one guidelines may serve as a framework of evidence-based recommendations for MM patients as the base for the development of meta-tools for both guideline developers and clinicians.