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A core outcome domain set to assess cutaneous neurofibromas related to neurofibromatosis type 1 in clinical trials

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REiNS consortium

Francis S. Collins Scholars Program

Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

Objective

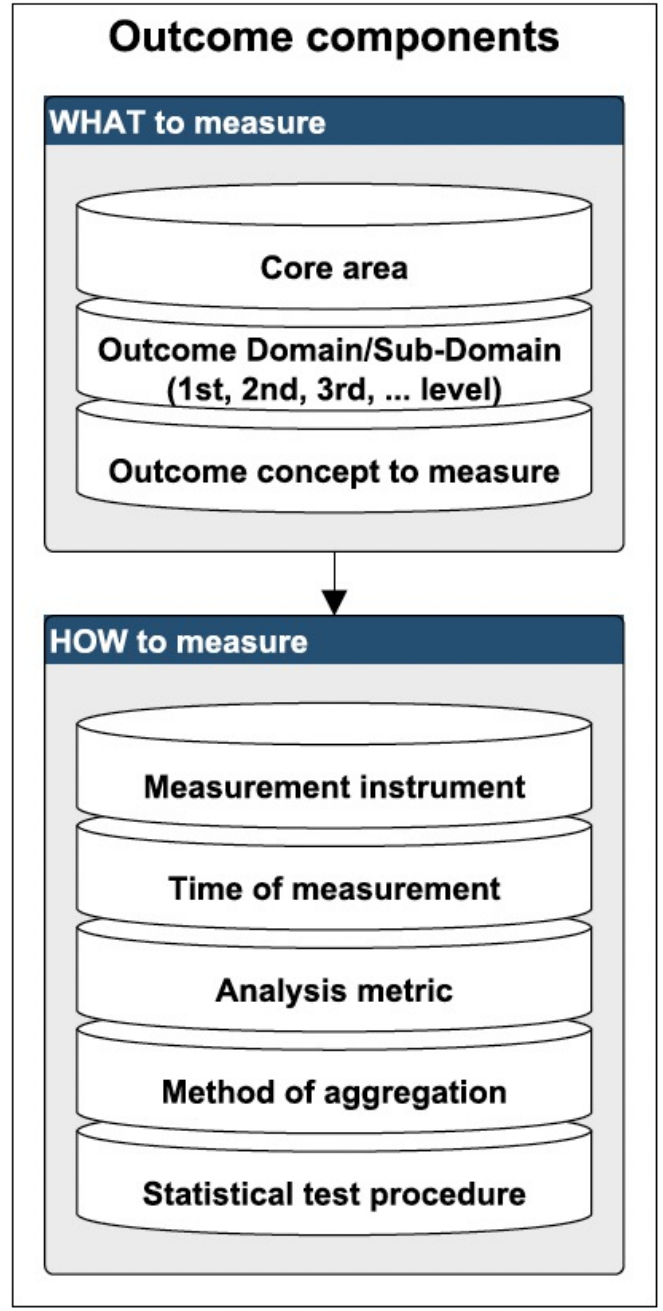
To avoid from the very beginning **lack of uniformity** in the outcomes reported in clinical studies of the treatment of cNF

To develop a **core outcome domain set (COS)**, a minimum set of an agreed set of datapoints that should be measured as a minimum in clinical trials for the treatment of cNF.

Will eventually allow **to compare trials**: to merge data in order to improve power, and to compare results between different trials and therapies.

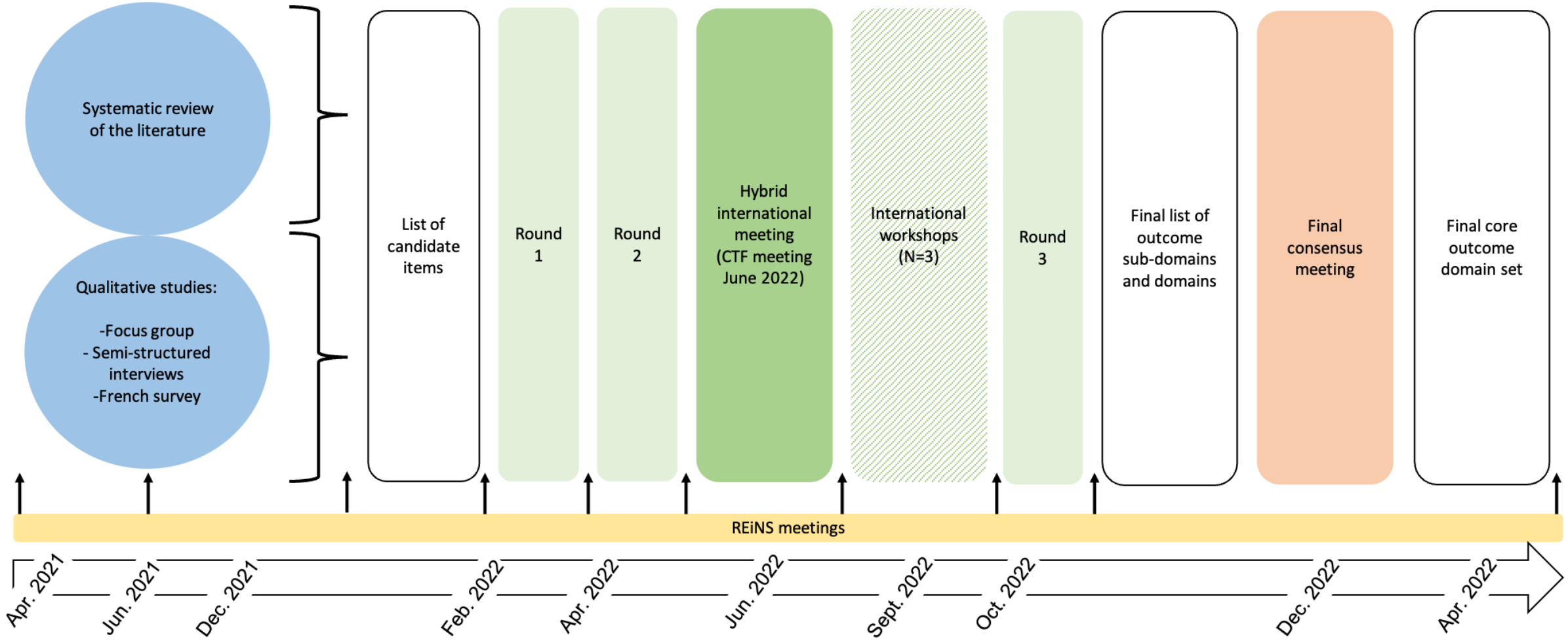
Methodology

- Guided by the recommendations of Core Outcome Measures in Effectiveness Trials (COMET), Outcome Measures in Rheumatology (OMERACT), and the Harmonizing Outcome Measures for Eczema (HOME) roadmap.
- Supported by the international CHORD COUSIN Collaboration (C3)
- The outcome components, defined as the “what to measure”, are usually classified as below, from the broadest to the most specific component



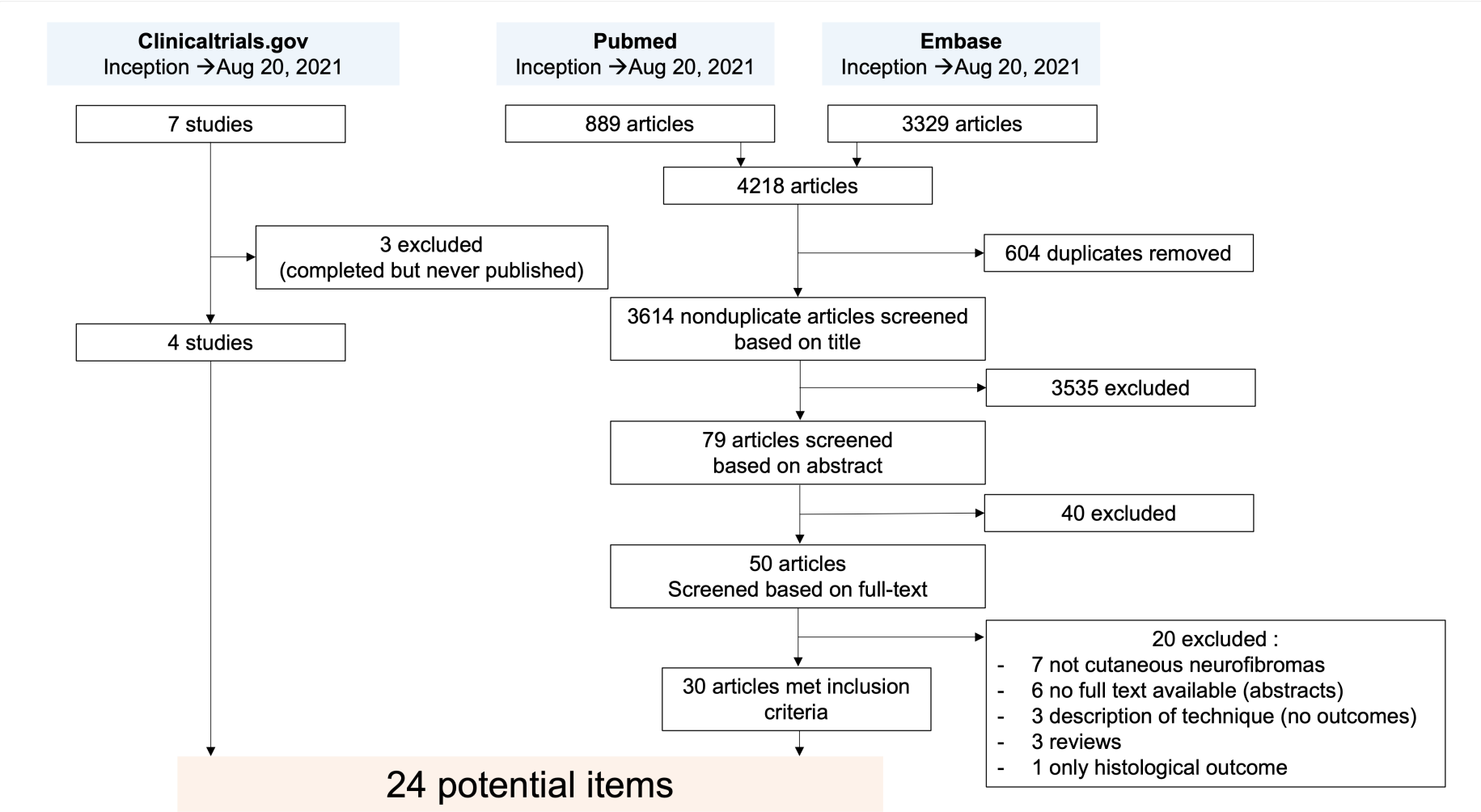
Lange et al. JEADV 2021

Summary of the study



The "generating" phase, **the "agreeing" phase**, and **the "voting" phase** of the process. The crosshatched pattern indicates the deviation of the initial protocol with the additional workshops which were not planned a priori (Europe, France and US).

Generating phase



The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. Results of the systematic literature review process focusing on outcomes reported in studies evaluating surgical and non-surgical interventions in cutaneous neurofibromas in Neurofibromatosis type 1.

Total of 31 potential items

Size and volume of cutaneous neurofibromas*†‡	Cosmesis related to cutaneous neurofibromas*†‡
Number of cutaneous neurofibromas*†‡	Health related quality of life*‡
Body surface area covered with of cutaneous neurofibromas‡	Physical functioning*‡
Color of cutaneous neurofibromas*†	Psychological functioning*†
Texture and consistency of cutaneous neurofibromas*†	Social functioning*†
Shape of cutaneous neurofibromas+	Stigma related to cutaneous neurofibromas‡
Overall skin texture*†	Self-esteem*†
Anatomic location of cutaneous neurofibromas *†‡	Self-image†
Visibility of cutaneous neurofibromas†‡	Intimacy*†
Pruritus caused by cutaneous neurofibromas*†‡	Clothing restrictions*†
Pain caused by cutaneous neurofibromas*†‡	Perceived severity related to cutaneous neurofibromas*‡
Irritation caused by cutaneous neurofibromas+	Satisfaction with treatment*‡
Recurrence of cutaneous neurofibromas*†‡	Treatment burden*†+
Stability of cutaneous neurofibromas†	Economic burden*†
Growth kinetics of cutaneous neurofibromas*+	Tolerability and adverse effects of treatments*†‡
	Wound healing from interventional treatment *‡

* items generated in systematic review of literature
† items generated by patient, psychologist and nurse coordinator interviews
‡ items generated by NF1 experts
+ items generated by NF1 patients (ComPaRe e-cohort)

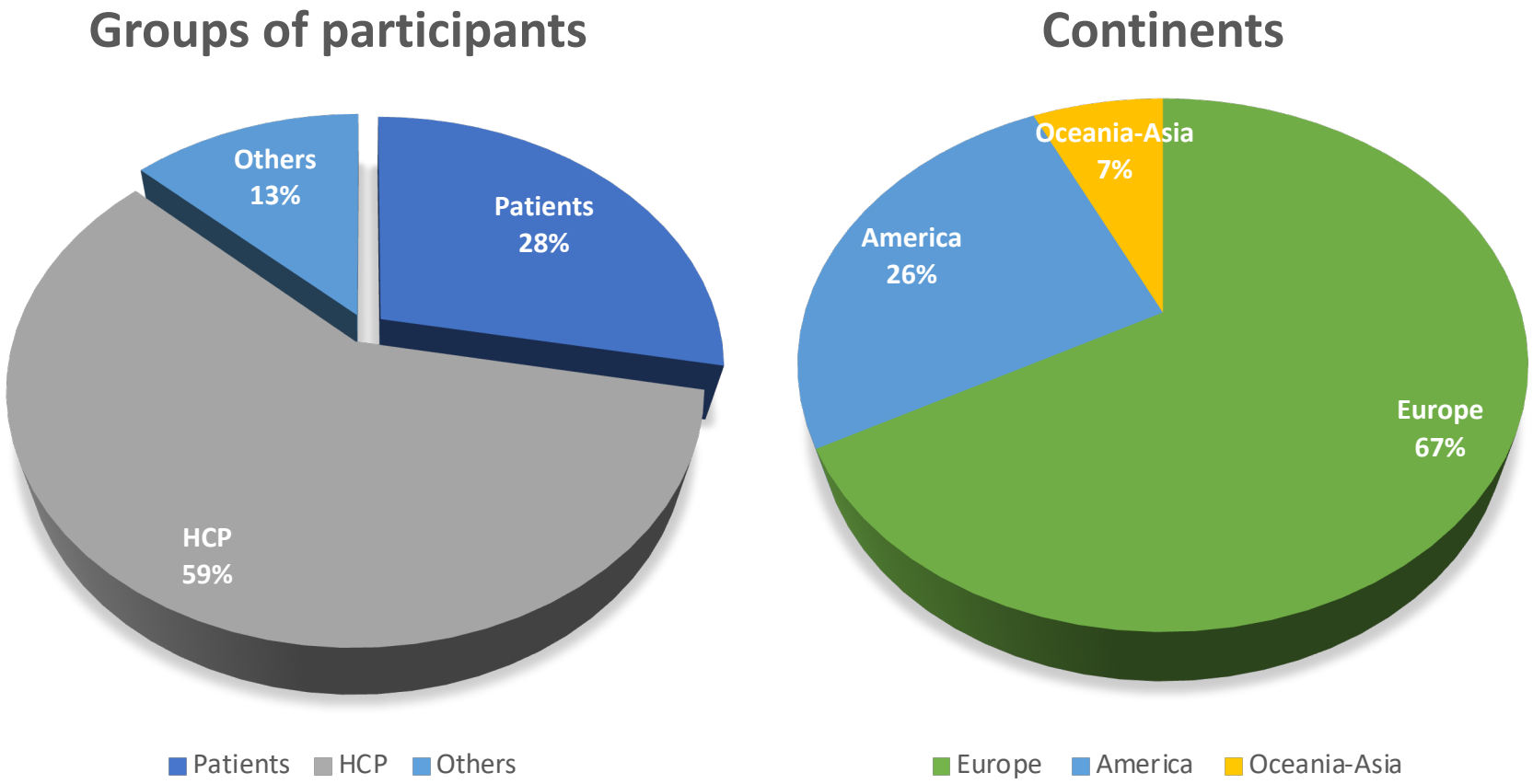
Agreeing phase

- **Three groups of stakeholders** were invited to participate:
  - G1: patients, relatives and representatives
  - G2: healthcare professionals (HCP)
  - G3: researchers, representatives of a drug regulatory authority, industry or pharmaceutical company representatives, and journal editors.
- **Anonymous international multi-perspective online Delphi**:
  - 3 rounds
  - Participants were asked to score the degree of importance of each of the listed potential items from 0 to 9

Classification	Description	Definition
Consensus in	The outcome will be retained in the consensus list	≥70% of participants rank the outcome 7-9 and less than 15% rank the outcome 1-3 .
Consensus out	The outcome will be removed from the consensus list	≥70% of participants rank the outcome 1-3 and less than 15% rank the outcome 7-9.
No consensus	The outcome will be of uncertain importance	Other situation.

Agreeing phase – E-Delphi

74% participation rate



Demographics of the participants of the e-Delphi. Group 1 (G1) included patients, patients' representatives and their relatives; group 2 (G2) included HCP; group 3 (G3) included researchers, representatives of a drug regulatory authority, industry or pharmaceutical company representatives, and journal editors.

Agreeing phase – E-Delphi

- Identification of **19 items as outcome sub-domains**.
- They were fused to create **4 outcome domains**: "clinical assessment", "daily life impact", "patient satisfaction" and "perception of health"
- They were **first prioritized according to the e-Delphi results**[1]:
  - Consensus in both groups: item important and required to be measured in all trials ("inner ring").
  - Consensus in only 1 or 2 groups: item important but not required to be measured in all trials ("middle ring").
  - No consensus in either of the groups ("outer ring"): item of uncertain importance and to be placed in the research agenda.

1. Callis Duffin et al. *JAMA Dermatol* 2018.

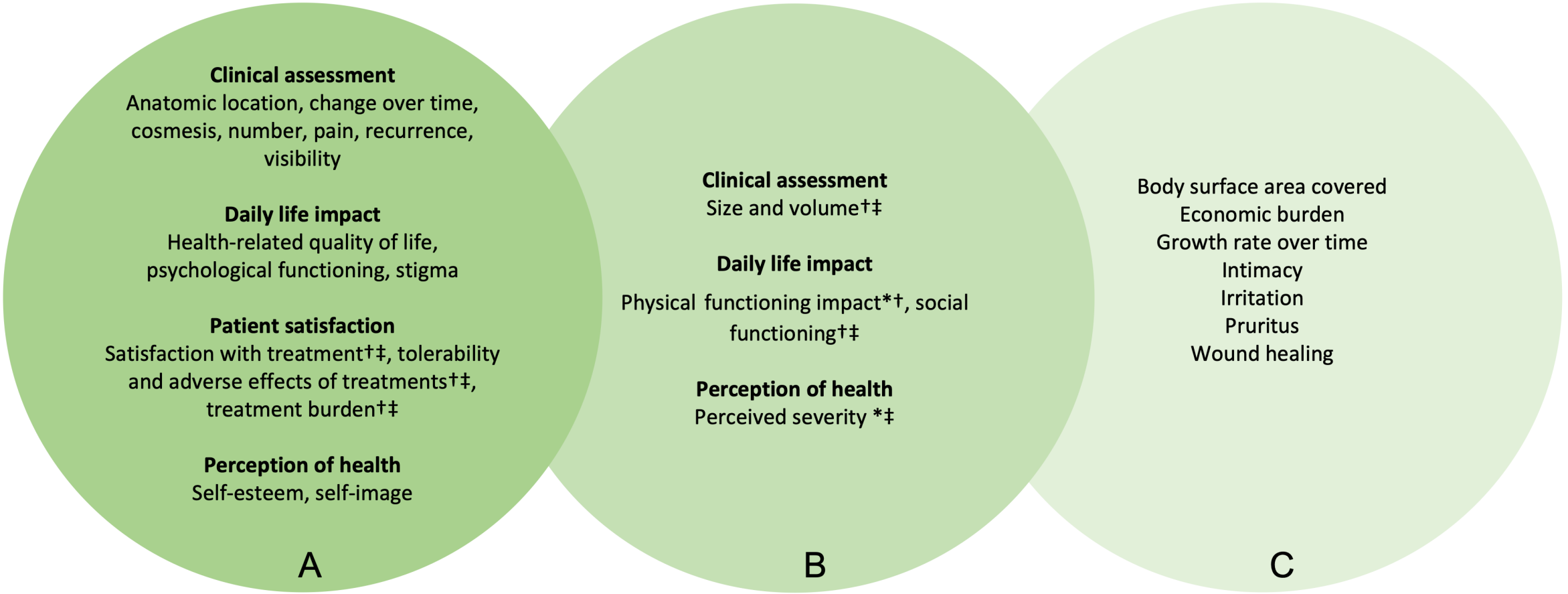
Voting phase

- The steering committee suggested one change in the prioritization:

  ➔ **moving the domain "patient's satisfaction" from the middle to the inner ring (including the sub-domains "tolerability and adverse effects").**

- The **final core outcome domain set reached 100% of the votes** of the 13 steering committee members.

Final core outcome domain set



The final core outcome domain set adapted from OMERACT onion model. The sub-domains reached consensus in G1*, G2† and G3‡.

Future roadmap

- To plan regular **updates of the core outcome domain set**
- **To develop and validate the corresponding measurement instruments**

Thank you for your attention

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