Embedding Qualitative Patient Interviews in Neurofibromatosis Clinical Trials to Facilitate Drug Development

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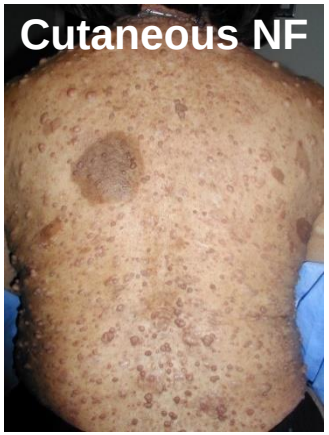
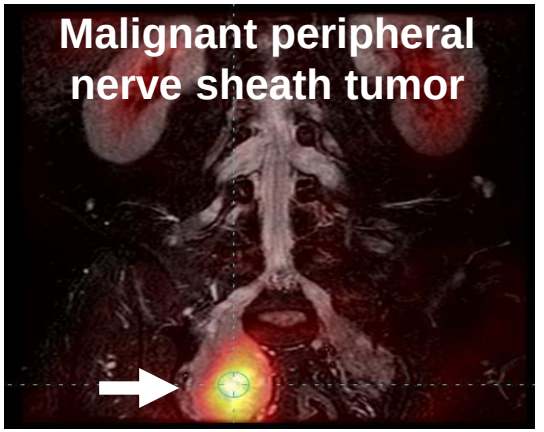
FDA Critical Path Innovation Meeting

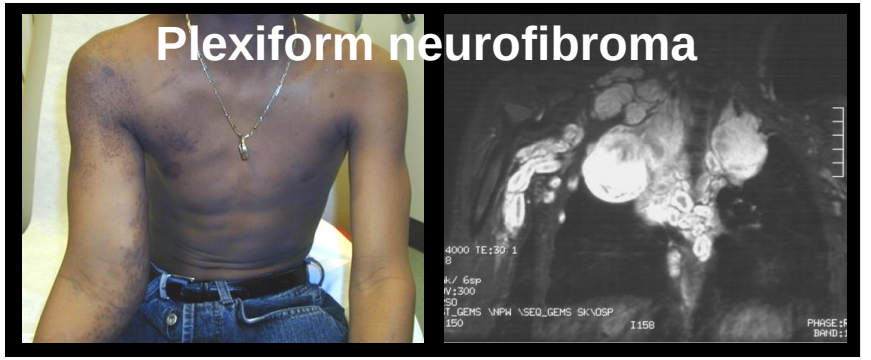
Response Evaluation In Neurofibromatosis Schwannomatosis
INTERNATIONAL COLLABORATION

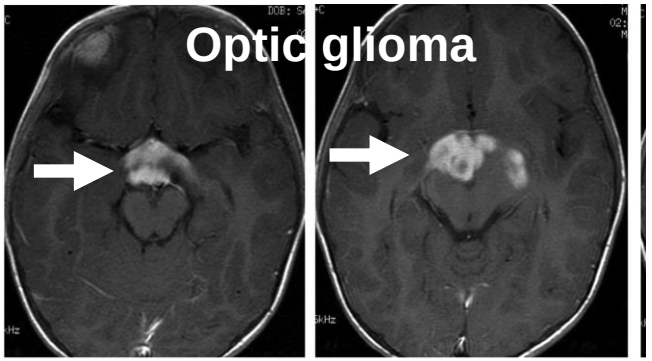
NF1 is a multisystem disorder

- Prevalence: 1 in 3000
- Caused by germline pathogenic variants in the *NF1* gene
- Average age at diagnosis: 1st decade
- Non-tumor manifestations
  - Cognitive/learning challenges
  - Impaired social functioning
  - Skeletal manifestations
  - Vasculopathy





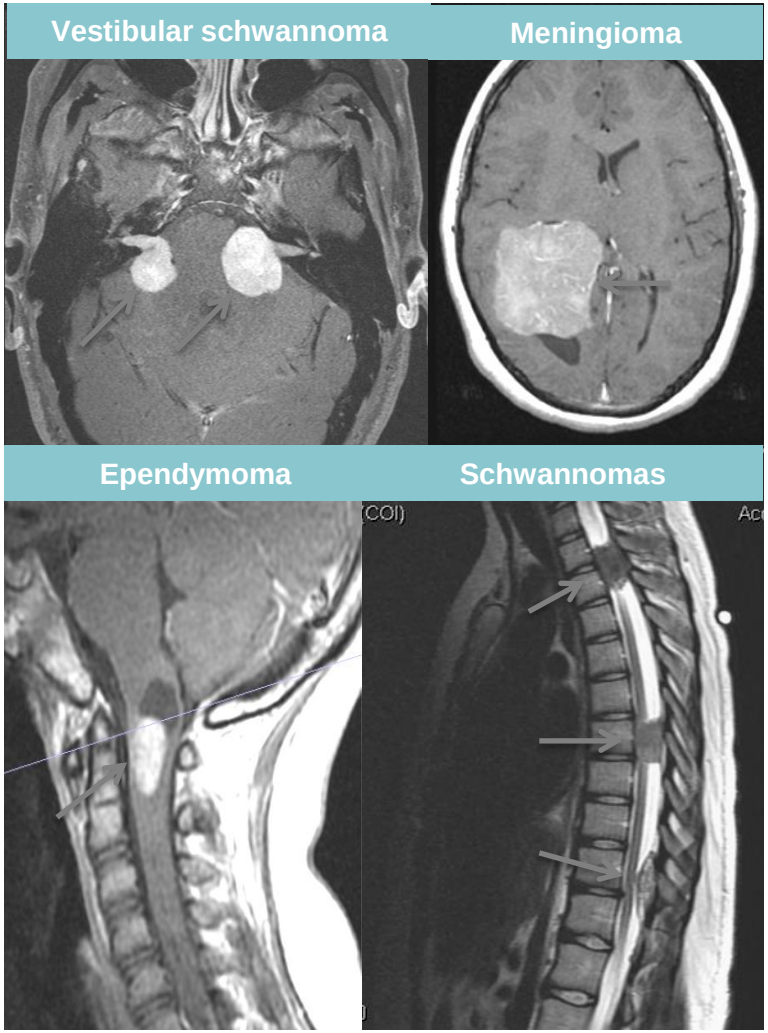




Evans et al, Am J Med Genet Part A 152A:327–332, 2009.

NF2 tumor suppressor syndrome

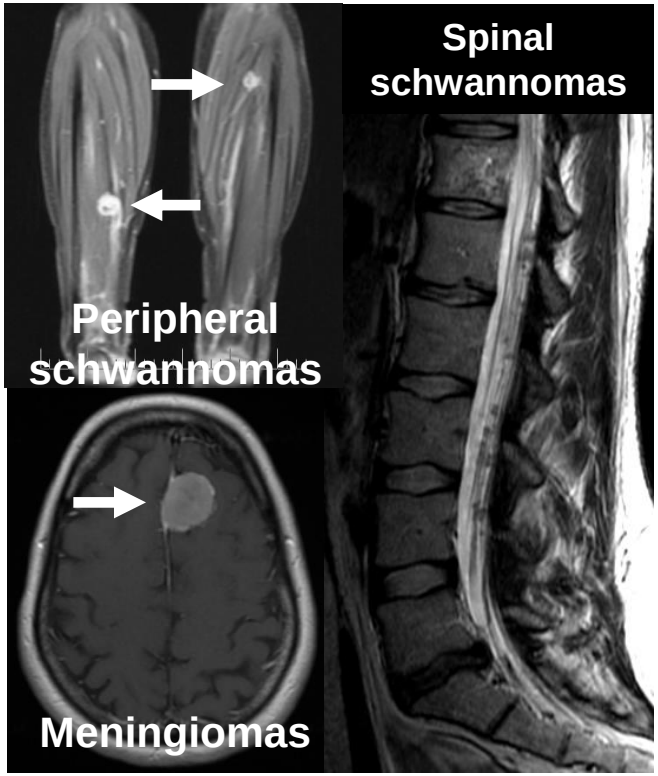
- Prevalence: 1 in 50,500
- Caused by germline pathogenic variants in the *NF2* gene
- Average age at diagnosis: 3rd decade
- Multiple tumors and tumor types
  - Schwannoma
  - Meningioma
  - Ependymoma
- Benign histology but not benign clinical course



Evans et al., Q J Med, 304, 603-618, 1992.
NF Consensus Statement, Arch. Neurol, 1988; 45: 575-8
Evans et al., J Neurol Neurosurg Psych, 2018

Schwannomatosis tumor suppressor syndrome

- Prevalence: 1 in 126,315
- Caused by germline pathogenic variants in the *SMARCB1, LZTR1* genes
- Average diagnosis--3rd/4th decade
- Typical presentation
  - Chronic pain > tumor mass
- Diagnosed by presence of multiple non-intradermal schwannomas
- Phenotype overlaps with NF2
- Chronic, severe pain is common



Evans et al., J Neurol Neurosurg Psych, 2018

REiNS International Collaboration

Response Evaluation in NF and Schwannomatosis

- Established in 2011 by team of investigators
- Goal: to develop standardized response criteria for determining treatment response in patients with NF1, NF2, and schwannomatosis
- Focus on collaboration
  - Across countries, institutions, and medical specialties
  - Among experts in NF and other specialties (including the Food and Drug Administration
  - Including patient representatives
- Consensus response criteria will improve our ability to measure and compare treatment efficacy
- Proactive discussion of endpoints with stakeholders will help facilitate approval of, and therefore access to, drugs for these rare conditions

Engaging stakeholders

- Investigators
- Patient representatives
- NF Foundations
- Food and Drug Administration
- Cancer Therapy Evaluation Program
- NIH/DOD
- Pharma

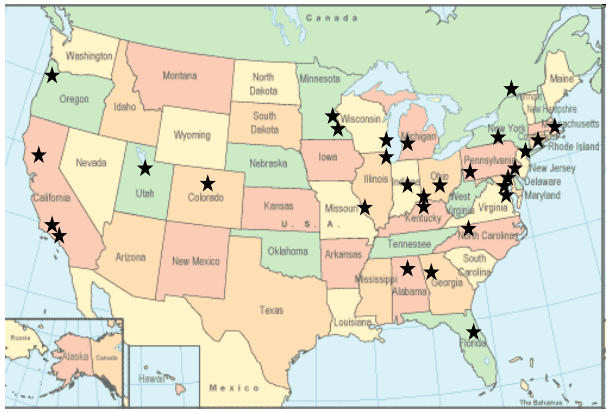
Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS)

Working groups

- Tumor Imaging (Widemann, Ahlawat)
- Functional outcomes (Plotkin)
- Patient reported outcomes (Merker)
- Visual outcomes (Avery, Fisher)
- Disease Biomarkers (Bettegowda/Hanemann)
- Neurocognitive outcomes (Janusz)
- Cutaneous neurofibromas (Cannon/Sarin)
- Patient Representation (Gross)

- 9 working groups
- Over 160 active members
- Over 70 institutions and organizations

The REiNS working groups are open to all participants



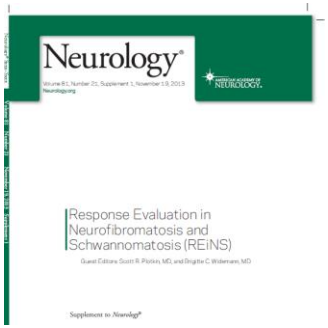
How REiNS Works

Working Groups → Full REiNS Collaboration → Published recommendations

- Monthly meetings
- Teleconference
- Develop recommendations

- Biannual meetings
- In person
- Review recommendations

- Every 2-3 years
- Neurology supplement



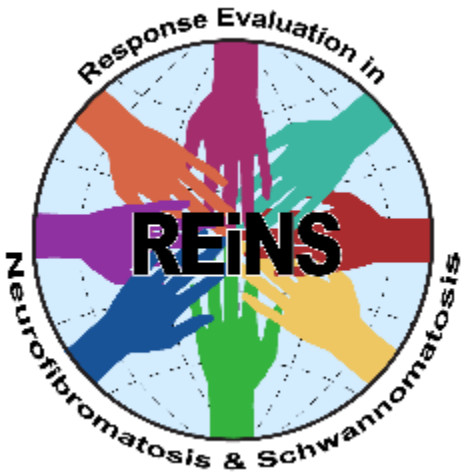
Collaborators:
- CTF and other foundations
- Food and Drug Administration
- Cancer Therapy Evaluation Program
- National Institutes of Health

REiNS publications (2013-2020)

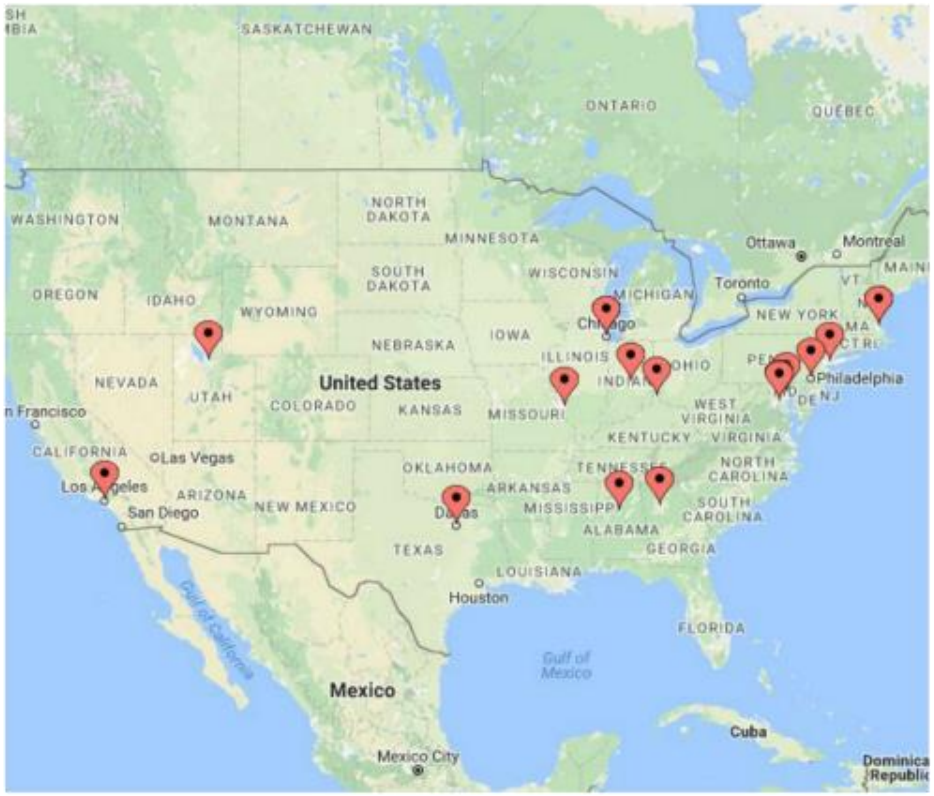
- Achieving consensus for clinical trials: The REiNS International Collaboration
- Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials
- Functional outcome measures for NF1-associated optic pathway glioma clinical trials
- Hearing and facial function outcomes for neurofibromatosis-2 clinical trials
- Recommendations for imaging tumor response in neurofibromatosis clinical trials
- Conclusions and future directions for the REiNS International Collaboration
- Consensus for NF Clinical Trials: Recommendations of the REiNS Collaboration
- Outcomes of Pain and Physical Functioning in NF Clinical Trials
- Sleep and pulmonary outcomes for clinical trials of airway plexiform neurofibromas in NF1
- Neurocognitive Outcomes in Neurofibromatosis Clinical Trials: Recommendations for the Domain of Attention
- Current Whole-Body MRI Applications in the Neurofibromatoses: NF1, NF2 and Schwannomatosis
- Current status and recommendations for biomarkers and biobanking in neurofibromatosis

13 manuscripts currently under review at Neurology journal

NF Research Ecosystem



Neurofibromatosis Clinical Trials Consortium



Clinical Trials for period 2007 – 2017

STOPN: Ph2 Study of Sirolimus in Plexiform Neurofibromas
STARS: Randomized, placebo study of lovastastin for learning disability
RAD001: Ph2 study of everolimus in low grade glioma
CABO: Ph2 study of cabozantinib for plexiform neurofibroma
MEK: Phase 2 Trial of MEK Inhibitor PD-0325901 in plexiform neurofibroma
NF2: Phase 2 study of bevacizumab for progressive VS in NF2
BMP2: Randomized study of Bone Morphogenetic Protein for Tibial Pseudarthrosis

Leadership:
Michael Fisher (Group chair)
Roger Packer (Group chair-past)
Bruce Korf (Coordinating Center)

Measurement Challenges in NF Trials

New Trial Indications

What to measure?
Supportive concepts to measure unclear

Measurement Challenges in NF Trials

Early in COA development

What to measure?
Supportive concepts to measure unclear
How to measure it?
Few validated symptom- or disease-specific quantitative outcome measures

Measurement Challenges in NF Trials

Wide age range

What to measure?
Supportive concepts to measure unclear
How to measure it?
Few validated symptom- or disease-specific quantitative outcome measures
Few quantitative measures that span the lifecourse

Measurement Challenges in NF Trials

Small, heterogenous samples

What to measure?
Supportive concepts to measure unclear
How to measure it?
Few validated symptom- or disease-specific quantitative outcome measures
Few quantitative measures that span the lifecourse
How to understand change in measures?
Limited ability to detect statistically significant changes in secondary outcomes

Measurement Challenges in NF Trials

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Usually no anchor-based MCID

Early in COA development

Measurement Challenges in NF Trials

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Supportive concepts to measure unclear
How to measure it?
Few validated symptom- or disease-specific quantitative outcome measures
Few quantitative measures that span the lifecourse
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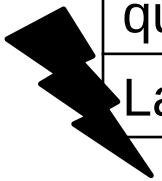
How to understand overall treatment impact?
May not be feasible to measure all impacts quantitatively

Multi-system disease

Measurement Challenges in NF Trials

What to measure?
Supportive concepts to measure unclear
How to measure it?
Few validated symptom- or disease-specific quantitative outcome measures
Few quantitative measures that span the lifecourse
How to understand change in measures?
Limited ability to detect statistically significant changes in secondary outcomes
Usually no anchor-based MCID
How to understand overall treatment impact?
May not be feasible to measure all impacts quantitatively
Lack of holistic, patient-centered view



NF Clinical Trial Examples

SPRINT
NF1: symptomatic, inoperable plexiform neurofibromas
Phase 2 registration trial
Open-label treatment
Historical controls

- Heterogenous population
- Many relevant secondary/tertiary outcomes

NF Clinical Trial Examples

SPRINT	INTUITT-NF2
NF1: symptomatic, inoperable plexiform neurofibromas	NF2: progressive, inoperable NF2-related tumors
Phase 2 registration trial	Screening platform/basket trial
Open-label treatment	Open-label treatment
Historical controls	No controls

- Heterogenous population
- Many relevant secondary/tertiary outcomes

- Few measures of how people feel or function
- Need to identify and refine relevant quantitative endpoints

NF Clinical Trial Examples

SPRINT	INTUITT-NF2	Tanezumab
NF1: symptomatic, inoperable plexiform neurofibromas	NF2: progressive, inoperable NF2-related tumors	Schwannomatosis: uncontrolled, moderate or severe chronic pain
Phase 2 registration trial	Screening platform/basket trial	Initial RCT
Open-label treatment	Open-label treatment	Double-blind followed by open-label treatment
Historical controls	No controls	Placebo control
• Heterogenous population • Many relevant secondary/tertiary outcomes	• Few measures of how people feel or function • Need to identify and refine relevant quantitative endpoints	• First ever trial in schwannomatosis • Unclear how best to define degree of meaningful change

Goals of Qualitative Patient Interviews

- Incorporate patient's perspectives more fully into our response evaluation
- Innovate new trial designs incorporating qualitative interviews to address these aims:
  - Refining quantitative endpoints for NF
  - Defining meaningful change
  - Demonstrating clinical benefits or harms
  - Informing overall risk/benefit analysis

INTUITT-NF2 Qualitative Sub-Study

- Platform/basket trial
  - Assessing multiple drugs (starting with brigatinib) for efficacy across four tumor types
- Outcome Measures:
  - Primary: ≥20% shrinkage in target tumor
  - Secondary: functional measures of hearing, quality of life PROM

INTUITT-NF2 Qualitative Sub-Study

- Qualitative Interview Goals
  - Document benefits and burdens of treatment
  - Assess content validity of PRO measure
  - Describe meaningful within-person change in PRO scores from NF2 patients' perspective
- Methodology
  - Hybrid concept elicitation/cognitive debriefing interviews
  - Interviews at ~6 months and ~12 months on treatment
  - Mixed-methods analysis

Ensuring Rigor in Qualitative Research

Patient-Focused Drug Development: Methods to Identify What Is Important to Patients

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

VALUE IN HEALTH 14 (2011) 967–977

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jval

ISPOR TASK FORCE REPORTS

Content Validity—Establishing and Reporting the Evidence in Newly Developed Patient-Reported Outcomes (PRO) Instruments for Medical Product Evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 1—Eliciting Concepts for a New PRO Instrument

Donald L. Patrick, PhD, MSPH[1,], Laurie B. Burke, RPh, MPH[2], Chad J. Gwaltney, PhD[3], Nancy Kline Leidy, PhD[4], Mona L. Martin, RN, MPA[5], Elizabeth Molsen, RN[6], Lena Ring, PhD[7]*

[1]Department of Health Services, University of Washington, Seattle, WA, USA; [2]Office of New Drugs, Center for Drug Evaluation Research, Food and Drug Administration,

International Journal for Quality in Health Care; Volume 19, Number 6: pp. 349–357
Advance Access Publication: 14 September 2007

10.1093/intqhc/mzm042

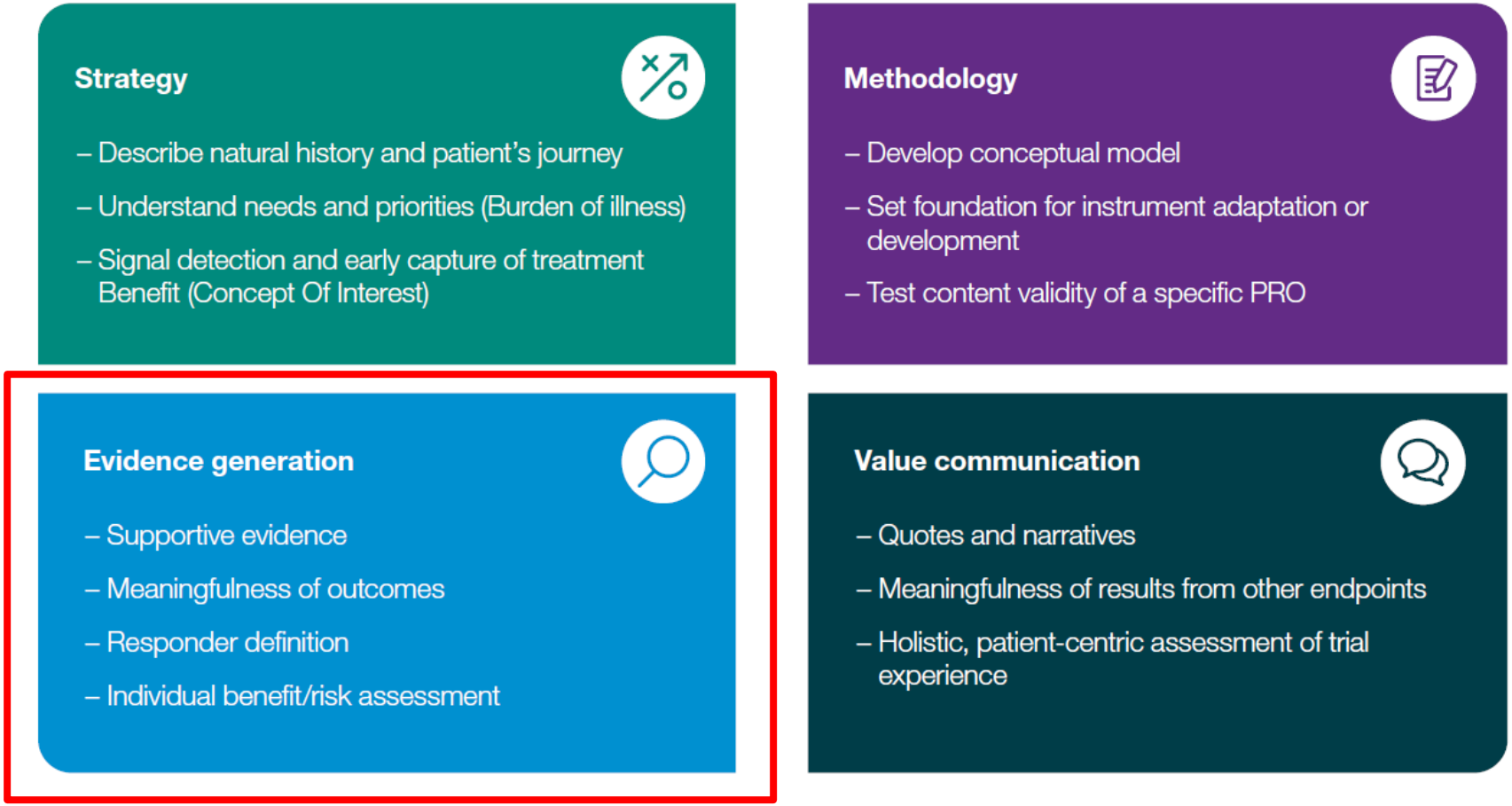
Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups

ALLISON TONG[1,2], PETER SAINSBURY[1,3] AND JONATHAN CRAIG[1,2]

[1]School of Public Health, University of Sydney, NSW 2006, Australia, [2]Centre for Kidney Research, The Children's Hospital at Westmead, NSW 2145, Australia, and [3]Population Health, Sydney South West Area Health Service, NSW 2170, Australia

Uses of Qualitative Data for Drug Development

Figure 2: Applications of qualitative research embedded in clinical trials



Capturing the voice of the patient in clinical trials: Why and how to integrate qualitative interviews into the protocol. White paper from ICON, available at www.ICONplc.com/pro

Discussion Question 1

Defining the role of qualitative data to supplement traditional quantitative data in rare diseases

Refining endpoints for NF:

How can qualitative data on treatment response from early trials best support the relevance/ meaningfulness of quantitative clinical outcome assessments chosen for use in subsequent trials?

Discussion Question 2

Defining the role of qualitative data to supplement traditional quantitative data in rare diseases

<u>Defining meaningful change</u>:

How can qualitative data on patients' perceptions of meaningful change best be elicited and used to contextualize the degree of benefit/harm they experience and to develop minimally clinically important differences for quantitative measures?

Discussion Question 3

Defining the role of qualitative data to supplement traditional quantitative data in rare diseases

<u>Demonstrating clinical benefit and harm</u>:

How can qualitative data best support claims of clinical benefit and understanding of treatment harms (including risk perception of potential harms and burden of side effects/adverse events)?

Discussion Question 4

Defining the role of qualitative data to supplement traditional quantitative data in rare diseases

<u>Informing overall risk/benefit analysis</u>:

How can qualitative data on patient's perceptions of the trade-offs between treatment benefits and harms inform FDA's consideration of a drug's overall risk/benefit profile?

Discussion Question 5

Understanding the appropriate clinical trial context to produce meaningful qualitative data

How can we embed qualitative research in clinical trials designed to overcome challenges of drug development in rare disease, such as:

- single-arm Phase 2 trials
- trials with open-label treatment
- platform and basket trials
- N-of-one trials?