Summary Report SPIRIT-PRO Extension

Delphi Round 1

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Section 1 Delphi panellist contact details and link to Round 1 Survey

Name:

Dear xxxx,

Delphi Panel ID:

Link to your Round 1 completed survey:

Your Email Address:

Attached is a copy of the information collected from the Stakeholder and Delphi Panel Surveys, within each table is a copy of your scores for that item. Please use the link above to return to your Round 1 Delphi Panel Survey responses.

Delphi Panel Round 2:

1) Please review this document and for each candidate SPIRIT-PRO item decide if you wish to **retain or amend your original scoring**.

2) If you wish to **amend your scoring** for any item, you may do so using the above link, which will allow you to edit your original Delphi survey answers until 28th February 2017. After this date, all data will be locked and will be taken forward to inform the international consensus meeting in May 2017.

3) If, after reviewing the attached results, you wish to **retain your original scores**, you do not need to do anything further. We will automatically take your existing data forward to the consensus meeting without further modification.

* All candidate items **where ≥70% of the panel have scored 7-9 (critical) and ≤15% have scored 1-3 (not important)** will automatically be taken forward for consideration at the consensus meeting. Borderline items will also be discussed. Following the consensus meeting we will circulate the draft SPIRIT-PRO for consultation prior to publication.

Many thanks for your input and support for the SPIRIT-PRO Initiative.

Summary Report SPIRIT-PRO Survey Results

Contents

Section 2 Recruitment Information

Stakeholders were contacted by gatekeepers from different organisations, these organisations were given a unique ID and responders to the stakeholder survey were asked to use that ID so that referring stakeholder groups could be identified. The largest recruiting group included ISOQOL and ISPOR.

Table 2.1 Stakeholder Recruitment Groups

Stakeholder Survey ID included in their email link		Response Percent	Response Total
1	ABPI (The Association of the British Pharmaceutical Industry)	0.72%	1
2	ChRN_PRO (Cochrane PROs Methods Group)	5.07%	7
3	COMET (Core Outcome Measures in Effectiveness Trials)	0.00%	0
4	CERTN (Comparative Effectiveness Research Translation Network)	0.72%	1
5	COSMIN (Consensus-based Standards for the selection of health Measurement Instruments)	7.97%	11
6	ECRIN (European Clinical Research Infrastructure Network)	0.72%	1
7	EMA (European Medicines Agency)	1.45%	2
8	EORTC (European Organisation for Research and Treatment of Cancer)	1.45%	2
9	ESC (European Society of Cardiology)	0.00%	0
10	HRA (Health Research Authority)	0.00%	0
11	INTDbF (International Diabetes Federation)	0.00%	0
12	ISPOR (International Society for Pharmoeconomics and Outcomes Research)	25.36%	35
13	ISOQoL (International Society for Quality of Life Research)	18.84%	26
14	MHRA (Medicines & Healthcare Products Reg Agency)	2.90%	4
15	MRCTMO (MRC Hubs for Trials Methodology Research Outcomes Working Group)	3.62%	5
16	NICE (National Institute for Health and Care Excellence)	0.72%	1
17	NIH (National Institute of Health)	2.90%	4
18	NIHR_PPI (National Institute for Health Research PPI initiative)	5.07%	7
19	SCT (Society for Clinical Trials)	9.42%	13
20	UKCRC (UKCRC Registered CTU Network)	5.07%	7
21	(AFNet) German Competence Network on Atrial Fibrillation	0.72%	1
22	ASCOT (American Surgical Collaborative and Trialist Group)	0.00%	0
23	BMJ (British Medical Journal)	0.00%	0
24	CCT (Canadian Cancer Trial)	0.72%	1
25	CRN (Clinical Research Network)	0.72%	1
26	DDR (Drug Development & Regulation Group)	0.00%	0

27	EFGCP (European Forum for Good Clinical Practice)	0.00%	0
28	EQ_N (Equator Network)	0.00%	0
29	GCanAPRE (Gov of Canada Interagency Advisory Panel on Research Ethics)	0.72%	1
30	INVOLVE	0.00%	0
31	AusCTN (Australian Cancer Trials Network)	0.00%	0
32	Lancet	0.00%	0
33	Macmlln (Macmillan)	0.00%	0
34	NCRI_Can (National Cancer Research Institute Canada)	0.00%	0
35	NCRI_CF (NCRI Consumer Forum)	1.45%	2
36	NHMRCAus (National Health & Med Research Council Australia)	0.00%	0
37	Rasch Experts Group (RaschEG)	1.45%	2
		answered	138

Other groups represented

NIHR Central Commissioning Faculty Patient and Public Involvement Team, Clinical Trials Unit; NorCrin

Section 3 Respondents Clinical Trial and PRO Research Experience

Table 3.1 Stakeholder group experience in clinical trials and PRO evaluation and development

Stakeholder Please tell us about your PRO, clinical trial and health research experiences			
		Response Percent	Response Total
Q4.1	I have experience in developing, implementing or reviewing PRO and clinical trials	82.73%	114
Q4.2	I have experience in developing or reviewing PRO through patient and public involvement	12.95%	18
Q4.3	Other (please specify):	4.32%	6
Other	Systematic Reviews; Developing and Reviewing PRO in a consultancy setting; Multinational Clinical trials; Development of Core Outcome Sets; Linguistic Validation of PRO		
	Total		138

Table 3.2 Delphi panel experience in clinical trials and pro evaluation and development

Q4 Delphi Please tell us about your PRO and clinical trial experiences			
		Response Percent	Response Total
Q4.1	I have experience in developing, implementing or reviewing PRO and clinical trial protocols	87.88%	87
Q4.2	I have experience in developing or reviewing PRO through patient and public involvement	4.04%	4
Q4.3	Other (please specify):	8.08%	8
Other	Regulator (Medical Assessor - MHRA); Expert in PRO development and evaluation; Helping to develop a drug which can alleviate the symptoms of Sjogrens syndrome; Behavioral scientist examining quality of life outcomes; Outcomes Research; NIAMS Clinical Trials Study Section member; Regulator; Medicines regulator		
	Total		99

Table 3.3 Stakeholder group years of experience in clinical trials and PRO evaluation and development

Q5 Stakeholder time spent in Clinical Trials and PRO Evaluation and Development					
	Less than 1 year	**1 to 5 years**	**6 to 10 years**	**More than 10 years**	**Response Total**
	N…(%)	N(%)	N(%)	N(%)	N
Q5.1 Experience in clinical trials	15 (11.0)	30 (22.1)	30 (22.1)	61 (44.9)	136
Q5.2 Experience in PRO protocol development or evaluation	9 (6.8)	45 (33.8)	34 (25.6)	45 (33.8)	133

Table 3.4 Delphi panel years of experience in clinical trials and PRO evaluation and development

Q5 Delphi time spent in Clinical Trials and PRO Evaluation and Development.					
	Less than 1 year	**1 to 5 years**	**6 to 10 years**	**More than 10 years**	**Response Total**
	N(%)	N(%)	N(%)	N(%)	
Q5.1 How many years experience do you have in clinical trials or health related research?	2(2.1)	8(8.2)	12(12.4)	75(77.3)	97
Q5.2 How many years experience do you have in PRO protocol development or evaluation?	9(9.5)	20(21.1)	14(14.7)	52(54.7)	95

The majority of the responders in both the Delphi and stakeholders groups have more than 10 years of experience in clinical trials evaluation and development. Experience of specific protocol development or evaluation of PRO varied with experience more evenly distributed across the range in the stakeholder group in comparison with the Delphi panel where more than 50% of the panel had more than 10 years of experience.

Figure 3.1 Stakeholder group number of clinical trials protocols developed or evaluated

Q6 Approximate No of clinical trial protocols respondents had been involved in developing or evaluating			
		Response Percent	Response Total
1	Less than 10;	42.34%	58
2	11 to 20;	15.33%	21
3	21 to 30;	15.33%	21
4	More than 30	27.01%	37
	Answered		137
	No response		1

Figure 3.2 Delphi panel number of clinical trials protocols developed or evaluated

Q6 Approximately how many clinical trial protocols have you been involved in developing or evaluating?			
		Response Percent	Response Total
1	Less than 10;	25.77%	25
2	11 to 20;	17.53%	17
3	21 to 30;	10.31%	10
4	More than 30	46.39%	45
	Answered		97
	No response		2

The majority of Stakeholder responders had developed or evaluated less than 10 clinical trial protocols in comparison to the Delphi Panel where over 46% had developed or evaluated more than 30 clinical trial protocols.

Figure 3.3 Primary Roles and Research Experience in Stakeholder Group

Q7 Stakeholder primary area of research experience

		Response Percent	Response Total
1	Clinician	7.97%	11
2	Clinical trial/health related academic/researcher	31.16%	43
3	Health Economist	5.80%	8
4	Statistician	9.42%	13
5	Trials methodologist	6.52%	9
6	Trial manager/coordinator	0.72%	1
7	Data manager/coordinator	0.72%	1
8	Research nurse/therapist	2.17%	3
9	Patient advocate	4.35%	6
10	Expert advisor on PROs in trials	7.97%	11
11	Psychometrician	5.80%	8
12	Funder	0.72%	1
13	Industry representative	2.17%	3
14	Journal editor	0.00%	0
15	Policy maker	0.72%	1
16	Ethicist/member of an ethical review panel	2.17%	3
17	Evidence synthesis researcher	3.62%	5
18	Other (please specify):	7.97%	11
		Answered	138
		No response	0

Other:

Mental Health User Consultant; Regulator; Health Psychologist; Set strategy, develop and validate measures, implement protocols, file market authorization documents, and publish results for a large pharma company: PRO Researcher in consultancy; PhD student: Linguistic validation of PRO; Reviewer; Regulator; Clinical Professor.

The majority of the stakeholder responders came from the Research group this consisted of health related academics, clinical trial and health related researchers. Clinicians, Statisticians and Expert advisor on PRO were the second largest groups.

Figure 3.4 Primary Roles and Research Experience in Delphi Panel

Q7 Delphi Panel primary area of research experience

		Response Percent	Response Total
1	Clinician	9.09%	9
2	Clinical trial/health related academic/researcher	24.24%	24
3	Health Economist	2.02%	2
4	Statistician	10.10%	10
5	Trials methodologist	5.05%	5
6	Trial manager/coordinator	2.02%	2
7	Data manager/coordinator	0.00%	0
8	Research nurse/therapist	2.02%	2
9	Patient advocate	10.10%	10
10	Expert advisor on PROs in trials	8.08%	8
11	Psychometrician	6.06%	6
12	Funder	1.01%	1
13	Industry representative	0.00%	0
14	Journal editor	3.03%	3
15	Policy maker	3.03%	3
16	Ethicist/member of an ethical review panel	5.05%	5
17	Evidence synthesis researcher	1.01%	1
18	Other (please specify):	8.08%	8
		Answered	99
		No response	0

Other:

Regulator; Medical Assessor; Behavioural Scientist; Outcomes Research Expert; Clinical Trials Member

Figure 3.5 Stakeholder Additional Areas of Research Experience

Q8 Stakeholder group additional area(s) of research experience responders could choose more than one category

		Response Percent	Response Total
1	Clinician	29.46%	33
2	Clinical trial/health related academic/researcher	41.96%	47
3	Health Economist	12.50%	14
4	Statistician	13.39%	15
5	Trials methodologist	22.32%	25
6	Trial manager/coordinator	15.18%	17
7	Data manager/coordinator	13.39%	15
8	Research nurse/therapist	4.46%	5
9	Patient advocate	8.04%	9
10	Expert advisor on PROs in trials	16.96%	19
11	Psychometrician	11.61%	13
12	Funder	0.00%	0
13	Industry representative	8.93%	10
14	Journal editor	6.25%	7
15	Policy maker	1.79%	2
16	Ethicist/member of an ethical review panel	9.82%	11
17	Evidence synthesis researcher	15.18%	17
18	Other (please specify):	7.14%	8
		Answered	112
		No response	26

Other:

Director of a CTU; Epidemiologist ; Cross Cultural Validation; Linguistic Validation of PRO; Lay reviewer for clinical trials funding; Health Policy Consultant; Translational Science Public Disclosure Lead

Figure 3.6 Delphi Panel Additional Areas of Research Experience

Q8 Delphi Panel additional area(s) of research experience responders could choose more than one category			
		Response Percent	Response Total
1	Clinician	24.14%	21
2	Clinical trial/health related academic/researcher	37.93%	33
3	Health Economist	4.60%	4
4	Statistician	12.64%	11
5	Trials methodologist	22.99%	20
6	Trial manager/coordinator	2.30%	2
7	Data manager/coordinator	2.30%	2
8	Research nurse/therapist	3.45%	3
9	Patient advocate	6.90%	6
10	Expert advisor on PROs in trials	29.89%	26
11	Psychometrician	19.54%	17
12	Funder	5.75%	5
13	Industry representative	3.45%	3
14	Journal editor	17.24%	15
15	Policy maker	9.20%	8
16	Ethicist/member of an ethical review panel	10.34%	9
17	Evidence synthesis researcher	12.64%	11
18	Other (please specify):	12.64%	11
		Answered	87
		No response	12
Other:			
Funder multiple charities; Collective response from statistics and operations office; Research Policy and developing ethical guidelines; Qualitative methods; Ethics Research; Medical Scientist; Research Engagement Activities; Director of R&D in a teaching hospital; Communicating and disseminating the value, need for & funding of PRO research; Expert Advisor on Health State Utilities and Preference Based Measures; Medical products regulator			

Figure 3.7 Clinical Areas Represented by Stakeholder Group

Q9	Clinical Areas	Responses	Response %	Response Total
1	Burns and plastics		0.00	0
2	Cardiology		7.25	10
3	Care of the Elderly		10.14	14
4	Dementia		8.70	12
5	Dermatology		2.17	3
6	Emergency Medicine/Trauma		1.45	2
7	Endocrinology		5.07	7
8	Gastroenterology		7.25	10
9	General Practice		8.70	12
10	Haematology		7.97	11
11	Neonatal Care		2.17	3
12	Neurology		14.49	20
13	Neurosurgery		1.45	2
14	Obstetrics and Gynaecology		4.35	6
15	Oncology		44.20	61
16	Orthopaedics		12.32	17
17	Paediatrics		12.32	17
18	Palliative Care		7.97	11
19	Public Health		18.12	25
20	Rehabilitation		11.59	16
21	Renal Medicine		5.07	7
22	Respiratory Medicine		7.25	10
23	Rheumatology		10.14	14
24	Sports and Exercise Medicine		3.62	5
25	Surgery		8.70	12
26	Other (please specify):		22.46	31
			Answered	138
			No response	0

Other:
Literacy ; Equity Mental health, Mental Health; Disability, Long term conditions; Aphasia; Psychology; Autism; Service Delivery Innovation; Adverse drug events; Opthalmology; Critical Care; Holistic Care; HIV; Neurodevelopmental disorders; Stem Cell Transplantation; Cancer Genetics; Spiritual wellbeing in Palliative Care; Generic Quality of Life; Urology; Psychiatry; Neurological movement disorders; Paediatric Otolaryngology; Family caregivers.

Over 45% of the stakeholder responders had a background in oncology; however all of other clinical areas were represented except for burns and plastics.

Figure 3.8 Clinical Areas Represented by Delphi Panel

Q9	Clinical Areas	Responses	Response %	Response Total
1	Burns and plastics		1.01	1
2	Cardiology		9.09	9
3	Care of the Elderly		9.09	9
4	Dementia		4.04	4
5	Dermatology		5.05	5
6	Emergency Medicine/Trauma		1.01	1
7	Endocrinology		5.05	5
8	Gastroenterology		10.10	10
9	General Practice		6.06	6
10	Haematology		12.12	12
11	Neonatal Care		2.02	2
12	Neurology		10.10	10
13	Neurosurgery		3.03	3
14	Obstetrics and Gynaecology		3.03	3
15	Oncology		56.57	56
16	Orthopaedics		4.04	4
17	Paediatrics		8.08	8
18	Palliative Care		16.16	16
19	Public Health		7.07	7
20	Rehabilitation		11.11	11
21	Renal Medicine		1.01	1
22	Respiratory Medicine		7.07	7
23	Rheumatology		17.17	17
24	Sports and Exercise Medicine		2.02	2
25	Surgery		15.15	15
26	Other (please specify):		17.17	17
			Answered	99
			No response	0

Other:

Psychiatry; Cachexia, Frailty & Sarcopenia; Musculoskeletal conditions; Editor of two general journals I've seen a wide range of trials and protocols; Pain management; Stem cell transplantation; Chronic disease; Evaluating perceptions of researchers using PROs; Urology; Sexual Health; None of these; Cover most of these as a funder; Orphan disease; Infectious diseases (HIV, Hepatitis); Rare diseases; Infectious diseases; All my experience with PROs and PROMs has been from the patient perspective; Additionally, I have few/limited experience with infectious diseases, multiple sclerosis and cardiovascular diseases; I am a patient I have read and edited PhD papers together with patient participation groups. Clinical trials study section; Pain in Children

Section 4 Stakeholder Participants Group Memberships

Figure 4.1 Group Memberships of the Stakeholder responders

Q10 Stakeholder Group Memberships		Responses	Response %	Response Total
1	UKCRC Reg CTU Network		7.56	9
2	ISOQOL		31.09	37
3	ISPOR		35.29	42
4	EMA		4.20	5
5	ECRIN		0.84	1
6	SCT		11.76	14
7	NIH		5.04	6
8	COMET		8.40	10
9	COSMIN		5.04	6
10	COCHRANE PRO GROUP		6.72	8
11	CERTAIN		0.84	1
12	International Diabetes Federation		0.84	1
13	EORTC		5.04	6
14	NICE		0.84	1
15	MRC Outcomes Working Group		1.68	2
16	ABPI		2.52	3
17	NIHR PPI CCF		5.04	6
18	NIHR		8.40	10
19	MHRA		4.20	5
20	HRA		2.52	3
21	Clinical Research Network		5.88	7
22	DDR (Drug Development & Regulation Group)		0.00	0
23	EFGCP (European Forum for Good Clin' Practice)		0.84	1
24	GCIAPRE (Government of Canada Interagency Advisory Panel on Research Ethics)		0.84	1
25	NHMRC (Nat' Health & Medical Research Council Australia)		0.00	0
26	INVOLVE		2.52	3
27	Macmillan Cancer Support		0.00	0
28	NCRI		0.84	1
29	NCRI Consumer forum		1.68	2
30	Australian Cancer Trials Network		0.84	1

31	Canadian Cancer Trials Group	0.00	0
32	EQUATOR Network	3.36	4
33	AFNet	0.00	0
34	ASCoT (American Surgical Collaborative and Trialist Group)	0.00	0
35	Other (please specify):	18.49	22
		Answered	119
		No response	19

Other:
OMERACT; ACC; ESC; FIMS; GCIG; SMDM; ISCTM;SCDM; CDISC;PHO; DIA; ACRP;ASNG;ASHE; British Psychological Society; MRC Conduct Hub; Medical Decision Making; Social Marketing; Drug Information Association; Iacrn; SoCRA; ONS; PCORI Reviewer; ASCO; International Union; International Union Against TB & Lung Disease; KT-Canada; Psychometric Society.

Participants were asked to identify which groups they belonged to over 60% of the responders were members of either ISOQOL (31%) and/or ISPOR (35%).

Figure 4.2 Group Memberships of Delphi Panel Members

Q10 Delphi Panel Group Memberships		Responses	Response %	Response Total
			Response Percent	Response Total
1	UKCRC Reg CTU Network		3.41	3
2	ISOQOL		52.27	46
3	ISPOR		18.18	16
4	EMA		4.55	4
5	ECRIN		2.27	2
6	SCT		9.09	8
7	NIH		9.09	8
8	COMET		9.09	8
9	COSMIN		4.55	4
10	COCHRANE PRO GROUP		9.09	8
11	CERTAIN		2.27	2
12	International Diabetes Federation		1.14	1
13	EORTC		10.23	9
14	NICE		1.14	1
15	MRC Outcomes Working Group		0.00	0
16	ABPI		1.14	1
17	NIHR PPI CCF		0.00	0
18	NIHR		9.09	8
19	MHRA		2.27	2
20	HRA		2.27	2
21	Clinical Research Network		4.55	4
22	DDR (Drug Development & Regulation Group)		1.14	1
23	EFGCP (European Forum for Good Clin' Practice)		5.68	5
24	GCIAPRE (Government of Canada Interagency Advisory Panel on Research Ethics)		0.00	0
25	NHMRC (Nat' Health & Medical Research Council Australia)		1.14	1
26	INVOLVE		1.14	1
27	Macmillan Cancer Support		3.41	3
28	NCRI		0.00	0
29	NCRI Consumer forum		2.27	2

30	Australian Cancer Trials Network	3.41	3
31	Canadian Cancer Trials Group	3.41	3
32	EQUATOR Network	5.68	5
33	AFNet	1.14	1
34	ASCoT (American Surgical Collaborative and Trialist Group)	0.00	0
35	Other (please specify):	27.27	24
		Answered	88
		No response	11

Other:

IPOS International Psycho-Oncology Society; None;CIHR / OMERACT/ was an ISOQOL PRP
BRS / NRAS; ONS, IACRN, SoCRA, ACRP; Health & Medical Research Fund, Govt. of Hong Kong; ASA; Other ethics which I doubt are relevant - BPA, SAP, ESOT; EHA SWG; ECOG; PCRC (Palliative Care Research Consortium); International Biometric Society; AGITG (Asutraliasian Gastro-Intestinal Trial Group); Patient Participation Group; UKONS (UK Oncology Nursing Society); iHEA - international health economics association, and HDCA - Human Development and Capability Association; SISAQOL; HRA; OMERACT; ICHOM; FDA; ASCO; EASL

Section 5 SPIRIT-PRO-Extension Candidate Checklist Items

The following section identifies the frequency that Stakeholder and Delphi panel survey respondents rated the relative importance of each of the SPIRIT- PRO extension checklist items. The responses were broken down into key stakeholder groups categorised from their identified primary roles.

- **Patient Rep** includes patient representatives, patients/public involved in research and patient advocates.
- **Researchers** includes clinical trial, health related academics and researchers, trial co-ordinators and data managers, participants working in PRO including linguistic translations.
- **Clinicians** includes clinicians, research nurse/therapists, health psychologists.
- **Methodologists** includes clinical trial and PRO methodologists and expert advisors.
- **Analysists** includes Psychometricians, statisticians, health economists.
- **Reviewers** includes journal editors, reviewers, funders, ethicists, regulators, policy makers, evidence synthesis researchers.

Included at the end column of each table is your score based on your responses to the Delphi Panel Stakeholder survey using your unique ID.

We ask you to review the information in relation to your own responses before editing your survey for Round 2 of the Delphi Panel exercise.

Those items scored as ≥70% 7-9 and ≤15% 1-3 will automatically be taken forward for consideration at the SPIRIT-PRO consensus meeting in May 2017.

Borderline items will also be considered at the meeting.

Following the meeting you will have opportunity to provide feedback on SPIRIT-PRO prior to publication.

Section 5 Delphi Panel Survey – Part 1
Context and Background to PRO

These sections relate directly to the SPIRIT-PRO Extension checklist items. Each section includes a description of the item and stakeholders responses overall and by summated professional groups. At the end of each table you can find your individual score for comparison.

Table 5.1 Responses to item #1 to item#5 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON SURVEY DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#1 List personnel responsible for PRO components of trial protocol	**Primary**	**Stakeholder**	8(5 to 8)	8(4 to 9)	8(6 to 9)	7(6 to 9)	7(6 to 9)	8(5 to 9)	**7(5 to 9)**	13.8	22.5	63.8	INCONCLUSIVE	
		Delphi	6(4 to 9)	8(5 to 9)	9(7 to 9)	8(5 to 9)	8(5 to 8)	7(4 to 9)	**8(5 to 9)**	8.1	27.3	64.6	INCONCLUSIVE	
	Secondary	**Stakeholder**	6(4 to 8)	6(4 to 8)	8(6 to 8)	6(5 to 7)	5(3 to 7)	6(5 to 8)	**6(4 to 8)**	16.7	40.6	42.8	INCONCLUSIVE	
		Delphi	6(4 to 7)	6(4 to 9)	7(6 to 9)	6(3 to 7)	6(4 to 7)	5(3 to 7)	**6(4 to 7)**	15.2	44.4	40.4	INCONCLUSIVE	
ITEM#2 Describe what is currently known about PROs in this area and explain the gaps in literature.	**Primary**	**Stakeholder**	7(5 to 8)	8(6 to 9)	8(6 to 9)	8(6 to 8)	7(6 to 8)	8(7 to 9)	**8(6 to 9)**	8.0	23.2	68.8	INCONCLUSIVE	
		Delphi	7(6 to 9)	9(8 to 9)	8(6 to 9)	9(8 to 9)	8(7 to 9)	8(7 to 9)	**8(7 to 9)**	4.0	11.1	84.8	INCLUDE	
	Secondary	**Stakeholder**	6(4 to 8)	6(4 to 7)	7(5 to 8)	7(5 to 8)	6(4 to 7)	7(5 to 8)	**6(4 to 7)**	13.8	44.2	42.0	INCONCLUSIVE	
		Delphi	5(4 to 8)	6(5 to 8)	6(5 to 7)	7(4 to 9)	6(5 to 7)	6(3 to 7)	**8(7 to 9)**	11.1	43.4	45.5	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON SURVEY DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#3 Provide a rationale for the inclusion of PROs as appropriate to the study population, intervention, context, objectives and setting.	**Primary**	**Stakeholder**	7(6 to 8)	9(7 to 9)	9(8 to 9)	9(8 to 9)	8(7 to 9)	9(8 to 9)	**9(7 to 9)**	2.2	10.1	87.7	**INCLUDE**	
		Delphi	7(6 to 9	9(8 to 9)	9(7 to 9)	9(9 to 9)	9(8 to 9)	8(6 to 9)	**9(8 to 9)**	2.0	10.2	87.8	**INCLUDE**	
	Secondary	**Stakeholder**	7(5 to 8)	7(5 to 9)	7(7 to 9)	8(7 to 9)	7(6 to 9)	7(6 to 9)	**7(6 to 9)**	2.2	34.1	63.8	**INCONCLUSIVE**	
		Delphi	6(5 to 7)	7(6 to 9)	8(7 to 9)	8(5 to 9)	7(7 to 9)	7(4 to 8)	**7(6 to 8)**	8.2	29.6	62.2	**INCONCLUSIVE**	
ITEM#4 State the PRO study objective in relation to PRO domain/s, patient population and timeframe.	**Primary**	**Stakeholder**	7(6 to 9)	8(8 to 9)	9(7 to 9)	9(8 to 9)	8(7 to 9)	9(7 to 9)	**8(7 to 9)**	1.5	10.2	88.3	**INCLUDE**	
		Delphi	7(6 to 9)	9(8 to 9)	9(8 to 9)	9(8 to 9)	9(8 to 9)	8(7 to 9)	**9(8 to 9)**	1.0	6.2	92.8	**INCLUDE**	
	Secondary	**Stakeholder**	6(6 to 8)	7(5 to 9)	7(6 to 8)	8(6 to 9)	7(6 to 8)	7(6 to 9)	**7(6 to 9)**	2.9	35.3	61.8	**INCONCLUSIVE**	
		Delphi	5(5 to 7)	7(5 to 8)	9(7 to 9)	8(7 to 9)	8(7 to 9)	8(5 to 8)	**7(6 to 9)**	1.0	32.3	66.7	**INCONCLUSIVE**	
ITEM#5 State the PRO hypothesis and corresponding null hypothesis and to which outcome(s) the hypothesis relates.	**Primary**	**Stakeholder**	7(4 to 8)	9(7 to 9)	8(8 to 9)	9(8 to 9)	9(8 to 9)	9(7 to 9)	**9(7 to 9)**	1.5	10.2	88.3	**INCLUDE**	
		Delphi	8(5 to 9)	9(7 to 9)	9(9 to 9)	9(8 to 9)	9(8 to 9)	8(5 to 9)	**9(7 to 9)**	4.0	14.1	81.8	**INCLUDE**	
	Secondary	**Stakeholder**	6(5 to 7)	6(4 to 8)	7(6 to 8)	7(6 to 8)	7(5 to 9)	6(5 to 9)	**7(5 to 8)**	6.5	40.6	52.9	**INCONCLUSIVE**	
		Delphi	5(3 to 8)	6(4 to 7)	7(7 to 8)	7(6 to 9)	7(6 to 8)	5(4 to 7)	**7(5 to 8)**	12.2	37.8	50.0	**INCONCLUSIVE**	

Section 6 Methods

Table 6.1 Responses to item#6 to item#11 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#6 If PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the sampling method.	**Primary**	**Stakeholder**	7(4 to 9)	8(7 to 9)	8(7 to 9)	8(7 to 9)	9(7 to 9)	8(7 to 9)	8(7 to 9)	2.9	13.2	83.8	INCLUDE	
		Delphi	7(5 to 9)	9(8 to 9)	9(7 to 9)	9(7 to 9)	9(8 to 9)	7(6 to 9)	9(7 to 9)	2.1	12.5	85.4	INCLUDE	
	Secondary	**Stakeholder**	6(3 to 9)	7(5 to 8)	7(6 to 8)	7(6 to 9)	7(5 to 9)	6(4 to 9)	7(5 to 9)	5.8	36.5	57.7	INCONCLUSIVE	
		Delphi	6(4 to 9)	7(5 to 9)	7(6 to 7)	7(6 to 9)	8(7 to 8)	7(5 to 7)	7(6 to 8)	4.1	30.6	65.3	INCONCLUSIVE	
ITEM#7 State the inclusion/exclusion criteria for PRO endpoint(s) (e.g., language/reading requirements).	**Primary**	**Stakeholder**	9(7 to 9)	8(7 to 9)	9(7 to 9)	8(8 to 9)	9(8 to 9)	8(6 to 9)	8(7 to 9)	2.2	15.6	82.2	INCLUDE	
		Delphi	9(5 to 9)	9(8 to 9)	8(7 to 9)	9(8 to 9)	9(7 to 9)	8(7 to 9)	7(7 to 9)	2.0	13.1	84.8	INCLUDE	
	Secondary	**Stakeholder**	8(7 to 9)	7(5 to 8)	8(7 to 9)	8(5 to 9)	7(6 to 9)	6(5 to 8)	7(5 to 9)	7.4	32.6	60.0	INCONCLUSIVE	
		Delphi	7(4 to 9)	8(7 to 9)	7(6 to 7)	8(7 to 9)	8(7 to 9)	7(5 to 8)	7(6 to 9)	3.0	27.3	69.7	INCONCLUSIVE	
ITEM#8 Specify if PRO completion is a pre-randomisation	**Primary**	**Stakeholder**	8(6 to 9)	8(7 to 9)	9(7 to 9)	8(6 to 9)	8(7 to 9)	9(7 to 9)	8(7 to 9)	4.4	15.6	80.0	INCLUDE	
		Delphi	7(5 to 8)	9(7 to 9)	9(7 to 9)	9(7 to 9)	9(8 to 9)	7(5 to 9)	9(7 to 9)	5.1	17.2	77.8	INCLUDE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
eligibility requirement.	**Secondary**	**Stakeholder**	8(6 to 8)	7(5 to 8)	7(7 to 9)	7(5 to 9)	7(5 to 9)	7(5 to 8)	7(5 to 8)	9.6	29.6	60.7	INCONCLUSIVE	
		Delphi	5(5 to 7)	8(6 to 9)	8(4 to 9)	6(5 to 9)	9(5 to 9)	6(4 to 7)	7(5 to 9)	8.1	40.4	51.5	INCONCLUSIVE	
ITEM#9 Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint.	**Primary**	**Stakeholder**	8(7 to 9)	9(8 to 9)	9(8 to 9)	9(8 to 9)	9(8 to 9)	9(9 to 9)	9(8 to 9)	1.4	5.1	92.0	INCLUDE	
		Delphi	7(7 to 9)	9(9 to 9)	9(9 to 9)	9(9 to 9)	9(9 to 9)	9(7 to 9)	9(9 to 9)	1.0	2.0	97.0	INCLUDE	
	Secondary	**Stakeholder**	7(6 to 8)	8(7 to 9)	9(7 to 9)	9(8 to 9)	8(7 to 9)	9(8 to 9)	8(7 to 9)	2.9	14.7	82.4	INCLUDE	
		Delphi	7(6 to 9)	9(8 to 9)	9(7 to 9)	9(9 to 9)	9(8 to 9)	8(7 to 9)	9(7 to 9)	0.0	15.2	84.8	INCLUDE	
ITEM#10 Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom.	**Primary**	**Stakeholder**	8(6 to 9)	9(7 to 9)	9(8 to 9)	8(7 to 9)	9(8 to 9)	8(7 to 9)	9(7 to 9)	2.2	11.8	86.0	INCLUDE	
		Delphi	7(6 to 9)	9(8 to 9)	8(7 to 9)	9(8 to 9)	9(7 to 9)	7(7 to 9)	9(7 to 9)	2.0	11.1	86.9	INCLUDE	
	Secondary	**Stakeholder**	7(6 to 9)	8(6 to 9)	8(6 to 9)	7(6 to 9)	8(6 to 9)	7(6 to 9)	8(6 to 9)	4.4	30.1	65.4	INCONCLUSIVE	
		Delphi	6(5 to 7)	7(5 to 9)	7(6 to 8)	9(7 to 9)	7(6 to 9)	7(5 to 7)	7(6 to 9)	3.0	34.3	62.6	INCONCLUSIVE	
ITEM#11 Specify the time point(s) for PRO analysis (including the	**Primary**	**Stakeholder**	7(6 to 8)	9(8 to 9)	9(8 to 9)	9(8 to 9)	9(8 to 9)	8(7 to 9)	9(8 to 9)	1.5	8.0	90.5	INCLUDE	
		Delphi	8(6 to 9	9(9 to 9)	9(7 to 9)	9(9 to 9)	9(8 to 9)	8(7 to 9)	9(8 to 9)	0.0	8.3	91.7	INCLUDE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting:* ***≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'***				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
principle time point of interest) and provide the rationale for these.	**Secondary**	**Stakeholder**	7(6 to 7)	8(6 to 9)	8(7 to 9)	8(7 to 9)	8(6 to 9)	7(6 to 9)	8(6 to 9)	1.5	24.8	73.7	**INCLUDE**	
		Delphi	6(5 to 9)	8(5 to 9)	8(5 to 9)	9(7 to 9)	9(8 to 9)	7(5 to 9)	8(6 to 9)	1.0	27.1	71.9	**INCLUDE**	

Section 7 Methods: Timing of PRO Assessments/Sample Size

Table 7.1 Responses to item#12 to item#17 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						*OVERALL MEDIAN (IQR)*	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	***Patient Reps***	***Researchers***	***Clinicians***	***Methodologists***	***Analysts***	***Reviewers***	***All Stakeholders***	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#12 Include PRO assessments in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment	**Primary**	**Stakeholder**	9(7 to 9)	9(8 to 9)	6(7 to 9)	9(8 to 9)	9(8 to 9)	9(7 to 9)	9(8 to 9)	2.2	4.4	93.4	INCLUDE	
		Delphi	8(7 to 9)	9(9 to 9)	9(9 to 9)	9(9 to 9)	9(9 to 9)	8(7 to 9)	9(8 to 9)	1.0	2.0	97.0	INCLUDE	
	Secondary	**Stakeholder**	8(6 to 8)	9(7 to 9)	8(7 to 9)	9(7 to 9)	9(7 to 9)	7(6 to 9)	9(7 to 9)	2.9	12.5	84.6	INCLUDE	
		Delphi	6(5 to 8)	9(7 to 9)	9(8 to 9)	9(8 to 9)	9(8 to 9)	7(4 to 8)	9(7 to 9)	1.0	15.2	83.8	INCLUDE	
ITEM#13 Specify if baseline PRO assessment should be completed before randomisation	**Primary**	**Stakeholder**	8(7 to 9)	9(7 to 9)	9 (7 to 9)	9(7 to 9)	9(8 to 9)	8(7 to 9)	9(7 to 9)	5.8	1.2	83.9	INCLUDE	
		Delphi	8(7 to 9)	9(7 to 9)	9(9 to 9)	9(8 to 9)	9(8 to 9)	8(6 to 9)	9(7 to 9)	4.1	9.2	86.7	INCLUDE	
	Secondary	**Stakeholder**	8(6 to 8)	8(6 to 9)	8(7 to 9)	8(6 to 9)	8(6 to 9)	7(6 to 9)	8(6 to 9)	7.3	22.6	70.1	INCLUDE	
		Delphi	7(5 to 9)	8(6 to 9)	8(5 to 9)	9(6 to 9)	9(8 to 9)	7(5 to 9)	8(6 to 9)	6.1	22.4	71.4	INCLUDE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						*OVERALL MEDIAN (IQR)*	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	***Patient Reps***	***Researchers***	***Clinicians***	***Methodologists***	***Analysts***	***Reviewers***	***All Stakeholders***	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#14 Specify the targeted time and acceptable time windows for each PRO assessment	**Primary**	**Stakeholder**	8(6 to 9)	8(7 to 9)	9(7 to 9)	8(7 to 9)	8(7 to 9)	8(7 to 9)	8(7 to 9)	1.5	9.6	89.0	INCLUDE	
		Delphi	8(7 to 9)	9(8 to 9)	9(7 to 9)	9(7 to 9)	7(6 to 9)	7(6 to 9)	8(7 to 9)	2.0	17.2	80.8	INCLUDE	
	Secondary	**Stakeholder**	8(6 to 8)	8(6 to 9)	8(7 to 9)	8(6 to 9)	8(6 to 9)	7(6 to 9)	8(6 to 9)	2.9	23.5	73.5	INCLUDE	
		Delphi	7(6 to 9)	8(6 to 9)	8(5 to 9)	7(6 to 9)	7(6 to 7)	7(5 to 9)	7(6 to 9)	3.0	33.3	63.6	INCONCLUSIVE	
ITEM#15 If PROs are to be completed in the clinic: specify timing of PROM delivery in relation to clinical assessments (e.g. before/whilst/after seeing clinician and/or clinical assessments)	**Primary**	**Stakeholder**	8(8 to 9)	9(7 to 9)	7(6 to 9)	8(7 to 9)	8(7 to 9)	8(6 to 9)	8(7 to 9)	4.4	15.3	80.3	INCLUDE	
		Delphi	8(7 to 9)	8(6 to 9)	9(7 to 9)	9(7 to 9)	8(6 to 9)	7(6 to 9)	8(6 to 9)	4.1	21.4	74.5	INCLUDE	
	Secondary	**Stakeholder**	7(6 to 8)	8(6 to 9)	7(5 to 8)	8(5 to 9)	8(6 to 9)	7(5 to 9)	7(6 to 9)	6.6	27.0	66.4	INCONCLUSIVE	
		Delphi	7(6 to 9)	8(5 to 9)	7(7 to 8)	8(7 to 9)	7(5 to 9)	6(4 to 7)	7(6 to 9)	5.1	33.7	61.2	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						*OVERALL MEDIAN (IQR)*	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	***Patient Reps***	***Researchers***	***Clinicians***	***Methodologists***	***Analysts***	***Reviewers***	***All Stakeholders***	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#16 Justify the timing of PRO assessments. Scheduled PRO assessments should link to research questions, hypotheses, length of recall, disease/treatment natural history, planned analysis and time of comparison must be comparable for both arms	**Primary**	**Stakeholder**	8(7 to 9)	8(7 to 9)	9(6 to 9)	8(6 to 9)	8(6 to 9)	8(7 to 9)	8(6 to 9)	3.7	22.8	73.5	INCLUDE	
		Delphi	7(6 to 9)	8(7 to 9)	9(7 to 9)	9(7 to 9)	7(6 to 9)	7(7 to 9)	8(7 to 9)	4.1	16.5	79.4	INCLUDE	
	Secondary	**Stakeholder**	8(6 to 8)	7(5 to 9)	6(4 to 8)	7(5 to 8)	7(5 to 9)	7(6 to 9)	7(6 to 8)	7.4	33.3	59.3	INCONCLUSIVE	
		Delphi	7(5 to 9)	8(5 to 9)	8(5 to 9)	7(6 to 8)	7(6 to 7)	7(4 to 9)	7(5 to 9)	8.3	37.5	54.2	INCONCLUSIVE	
ITEM#17 If PRO is the primary endpoint, state the required PRO sample size, otherwise discuss the power of the	**Primary**	**Stakeholder**	8(7 to 9)	9(8 to 9)	9(7 to 9)	9(8 to 9)	9(8 to 9)	9(8 to 9)	9(8 to 9)	0.7	6.6	92.7	INCLUDE	
		Delphi	8(7 to 9)	9(9 to 9)	9(9 to 9)	9(8 to 9)	9(9 to 9)	8(7 to 9)	9(8 to 9)	0.0	7.1	92.9	INCLUDE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						*OVERALL MEDIAN (IQR)*	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	***Patient Reps***	***Researchers***	***Clinicians***	***Methodologists***	***Analysts***	***Reviewers***	***All Stakeholders***	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
PRO analyses	**Secondary**	**Stakeholder**	7(6 to 8)	6(4 to 8)	7(6 to 8)	8(5 to 9)	8(5 to 9)	7(4 to 9)	7(5 to 8)	11.4	33.3	55.3	**INCONCLUSIVE**	
		Delphi	7(to 8)	5(4 to 8)	4(2 to 9)	7(6 to 9)	6(5 to 9)	6(3 to 7)	6(4 to 8)	17.8	37.8	44.4	**INCONCLUSIVE**	

Section 8 Methods: PRO Instrument Description/Justification

Table 8.1 Responses to item#18 to item#22 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#18 Describe the PROMs including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, acceptability, recall period. Provide references as appropriate	**Primary**	**Stakeholder**	8(7 to 9)	8(6 to 9)	9(6 to 9)	8(6 to 9)	8(6 to 9)	7(5 to 9)	8(6 to 9)	3.7	25.7	70.6	INCLUDE	
		Delphi	7(6 to 9)	9(7 to 9)	9(6 to 9)	9(6 to 9)	9(7 to 9)	8(7 to 8)	8(7 to 9)	2.0	20.2	77.8	INCLUDE	
	Secondary	**Stakeholder**	7(6 to 8)	6(5 to 8)	7(5 to 8)	6(5 to 8)	6(5 to 9)	6(4 to 8)	6(5 to 8)	8.1	47.1	44.9	INCONCLUSIVE	
		Delphi	6(5 to 7)	7(4 to 9)	7(4 to 8)	7(5 to 9)	7(5 to 9)	6(5 to 8)	6(5 to 8)	6.2	45.4	48.5	INCONCLUSIVE	
ITEM#19 Justify choice of PROM(s) by linking specific domains/items	**Primary**	**Stakeholder**	7(6 to 8)	8(7 to 9)	8(6 to 9)	8(6 to 9)	8(6 to 9)	7(6 to 8)	8 (6 to 9)	1.5	25.5	73.0	INCLUDE	
		Delphi	7(6 to 9)	9(7 to 9)	8(4 to 9)	9(7 to 9)	8(7 to 9)	7(5 to 8)	8(7 to 9)	2.0	19.2	78.8	INCLUDE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
to clinical justifications and hypotheses	**Secondary**	**Stakeholder**	7(6 to 7)	6(5 to 8)	6(5 to 7)	7(5 to 9)	6(5 to 8)	7(6 to 7)	6(5 to 8)	5.1	46.7	48.2	INCONCLUSIVE	
		Delphi	6(5 to 9)	7(4 to 9)	6(4 to 8)	9(6 to 9)	7(5 to 7)	5(4 to 7)	7(5 to 8)	8.1	40.4	51.5	INCONCLUSIVE	
ITEM#20 Provide evidence of measurement equivalence across modes (i.e., when mixing modes of PRO data collection) and/or of cross cultural validity where different language versions of questionnaires are used)	**Primary**	**Stakeholder**	8(7 to 9)	8(7 to 9)	7(6 to 8)	8(6 to 9)	7(5 to 8)	7(5 to 8)	7(6 to 9)	7.3	24.1	68.6	INCONCLUSIVE	
		Delphi	8(7 to 9)	8(5 to 9)	5(3 to 7)	7(6 to 9)	7(5 to 9)	6(5 to 7)	7(5 to 8)	14.4	27.8	57.7	INCONCLUSIVE	
	Secondary	**Stakeholder**	7(6 to 8)	7(5 to 7)	6(5 to 7)	6(4 to 8)	6(4 to 8)	6(5 to 8)	6(5 to 8)	14.0	42.6	43.4	INCONCLUSIVE	
		Delphi	7(6 to 9)	6(4 to 9)	5(3 to 5)	6(4 to 7)	6(4 to 7)	5(3 to 6)	6(4 to 7)	19.6	45.4	35.1	INCONCLUSIVE	
ITEM#21 Outline plans	**Primary**	**Stakeholder**	7(6 to 8)	7(6 to 9)	7(5 to 9)	8(6 to 9)	8(5 to 9)	7(6 to 8)	7(6 to 9)	6.7	27.6	65.7	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
for evaluation of measurement properties, if appropriate (e.g. if not previously validated in the population of interest)		**Delphi**	7(5 to 9)	8(6 to 9)	7(3 to 8)	7(4 to 9)	9(6 to 9)	7(6 to 8)	7(6 to 9)	10.5	26.3	63.2	INCONCLUSIVE	
	Secondary	**Stakeholder**	7(6 to 7)	6(5 to 7)	6(3 to 8)	6(5 to 8)	6(3 to 8)	6(5 to 7)	6(5 to 8)	16.2	43.4	40.4	INCONCLUSIVE	
		Delphi	6(5 to 8)	5(3 to 9)	6(4 to 7)	6(4 to 7)	7(5 to 8)	5(4 to 6)	6(4 to 7)	17.2	45.2	37.6	INCONCLUSIVE	
ITEM#22 Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population	**Primary**	**Stakeholder**	7(5 to 8)	7(6 to 9)	7(5 to 9)	6(5 to 8)	6(5 to 8)	6(5 to 8)	7(5 to 8)	8.8	37.2	54.0	INCONCLUSIVE	
		Delphi	8(6 to 9)	7(5 to 9)	6(5 to 6)	7(6 to 8)	7(6 to 8)	7(5 to 8)	7(6 to 8)	5.1	40.4	54.5	INCONCLUSIVE	
	Secondary	**Stakeholder**	7(5 to 7)	6(4 to 8)	6(5 to 9)	6(4 to 7)	6(4 to 7)	5(5 to 6)	6(4 to 7)	15.6	50.4	34.1	INCONCLUSIVE	
		Delphi	6(4 to 8)	5(4 to 8)	5(4 to 6)	6(5 to 8)	6(4 to 7)	4(4 to 7)	5(4 to 7)	14.1	52.5	33.3	INCONCLUSIVE	

Section 9 Methods: PRO Data Collection

Table 9.1 Responses to item#23 to item#30 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#23 Include a pre-specified data collection plan.	**Primary**	**Stakeholder**	7(6 to 8)	8(7 to 9)	8(7 to 9)	8(7 to 9)	8(6 to 9)	8(7 to 9)	8(7 to 9)	4.4	19.9	74.6	INCLUDE	
		Delphi	7(6 to 9)	9(8 to 9)	8(6 to 9)	9(7 to 9)	8(6 to 9)	8(7 to 9)	9(7 to 9)	3.1	16.7	80.2	INCLUDE	
	Secondary	**Stakeholder**	6(5 to 7)	7(6 to 9)	7(6 to 9)	7(5 to 9)	7(5 to 9)	7(6 to 9)	7(6 to 9)	5.2	35.1	59.7	INCONCLUSIVE	
		Delphi	7(5 to 8)	9(6 to 9)	7(5 to 9)	8(7 to 9)	6(5 to 9)	7(4 to 8)	8(5 to 9)	8.4	28.4	63.2	INCONCLUSIVE	
ITEM#24 Specify how PROM will be completed (e.g. pencil and paper, online, etc).	**Primary**	**Stakeholder**	8(6 to 9)	8(6 to 9)	9(7 to 9)	8(6 to 9)	7(6 to 9)	7(5 to 8)	8(6 to 9)	2.9	26.5	70.6	INCLUDE	
		Delphi	8(7 to 9)	8(6 to 9)	9(8 to 9)	9(7 to 9)	8(6 to 9)	7(6 to 9)	8(7 to 9)	3.0	21.2	75.8	INCLUDE	
	Secondary	**Stakeholder**	7(6 to 8)	7(6 to 9)	8(7 to 9)	7(5 to 9)	6(4 to 9)	6(4 to 8)	7(6 to 9)	5.9	35.6	58.5	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
		Delphi	8(5 to 9)	8(5 to 9)	8(6 to 9)	9(7 to 9)	7(5 to 9)	7(4 to 7)	7(5 to 9)	7.1	28.6	64.3	INCONCLUSIVE	
ITEM#25 Specify where PROM will be completed (e.g. clinic, home, etc).	**Primary**	**Stakeholder**	8(6 to 8)	7(7 to 9)	8(6 to 9)	8(6 to 9)	8(6 to 9)	7(4 to 8)	8(6 to 9)	2.9	27.2	69.9	INCONCLUSIVE	
		Delphi	8(6 to 9)	8(6 to 9)	8(5 to 9)	9(7 to 9)	8(6 to 9)	7(6 to 9)	8(6 to 9)	4.0	25.3	70.7	INCLUDE	
	Secondary	**Stakeholder**	6(6 to 7)	7 (6 to 9)	7(6 to 9)	8(5 to 9)	6(5 to 9)	6(4 to 8)	7(6 to 9)	5.2	39.3	55.6	INCONCLUSIVE	
		Delphi	8(5 to 9)	7(5 to 9)	5(4 to 7)	8(6 to 9)	7(5 to 9)	7(4 to 8)	7(5 to 9)	7.1	37.8	55.1	INCONCLUSIVE	
ITEM#26 Where applicable, justify use of proxies (define conditions under which proxy assessment is	**Primary**	**Stakeholder**	7(6 to 9)	8(7 to 9)	9(7 to 9)	7(6 to 9)	8(7 to 9)	7(6 to 9)	8(7 to 9)	2.2	19.3	78.5	INCLUDE	
		Delphi	8(5 to 9)	8(7 to 9)	9(6 to 9)	9(7 to 9)	8(6 to 9)	7(5 to 9)	8(6 to 9)	5.2	21.6	73.2	INCLUDE	
	Secondary	**Stakeholder**	6(6 to 8)	7(5 to 9)	8(7 to 9)	7(5 to 8)	8(5 to 9)	7(6 to 9)	7(5 to 9)	4.5	33.1	62.4	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
permissible).		**Delphi**	5(5 to 9)	8(5 to 9)	7(5 to 9)	9(6 to 9)	7(5 to 9)	5(4 to 9)	7(5 to 9)	7.2	37.1	55.7	INCONCLUSIVE	
ITEM#27 Specify who will administer the PROM (e.g. a physician, nurse, etc).	**Primary**	**Stakeholder**	8(7 to 9)	8(7 to 9)	7(5 to 9)	6(3 to 8)	7(6 to 9)	7(5 to 9)	7(6 to 9)	11.7	25.5	62.8	INCONCLUSIVE	
		Delphi	8(6 to 9)	7(5 to 9)	6(3 to 9)	9(6 to 9)	7(4 to 8)	7(6 to 8)	7(5 to 9)	8.2	32.7	59.2	INCONCLUSIVE	
	Secondary	**Stakeholder**	7(6 to 8)	7(5 to 9)	7(5 to 9)	5(3 to 7)	7(5 to 8)	5(4 to 7)	7(5 to 8)	14.7	34.6	50.7	INCONCLUSIVE	
		Delphi	6(5 to 9)	6(4 to 9)	5(3 to 7)	7(5 to 9)	6(4 to 7)	6(4 to 7)	6(4 to 9)	11.3	45.4	43.3	INCONCLUSIVE	
ITEM#28 If it is permissible for another person to help the study participant complete the PROM, describe what	**Primary**	**Stakeholder**	7(7 to 9)	8(7 to 9)	9(7 to 9)	7(6 to 9)	7(6 to 9)	8(6 to 9)	7(6 to 9)	5.2	20.0	74.8	INCLUDE	
		Delphi	8(5 to 9)	8(6 to 9)	7(4 to 9)	9(7 to 9)	8(4 to 9)	7(4 to 9)	8(5 to 9)	10.1	27.3	62.6	INCONCLUSIVE	
	Secondary	**Stakeholder**	6(6 to 8)	7(6 to 9)	9(7 to 9)	7(5 to 7)	7(4 to 8)	6(5 to 9)	7(6 to 9)	6.7	32.1	61.2	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
type and level of assistance is acceptable.		**Delphi**	5(5 to 9)	7(5 to 9)	4(3 to 7)	8(6 to 9)	7(4 to 7)	6(4 to 6)	6(4 to 9)	13.1	39.4	47.5	INCONCLUSIVE	
ITEM#29 If more than one PROM will be used, specify whether the order of administration will be standardised or randomised.	**Primary**	**Stakeholder**	7(6 to 8)	7(6 to 9)	7(4 to 9)	8(6 to 9)	7(6 to 9)	7(4 to 8)	7(6 to 9)	7.4	30.4	62.2	INCONCLUSIVE	
		Delphi	7(6 to 9)	6(5 to 9)	5(3 to 8)	7(4 to 9)	7(4 to 9)	7(6 to 9)	7(5 to 9)	13.1	33.3	53.5	INCONCLUSIVE	
	Secondary	**Stakeholder**	7(6 to 7)	7(5 to 8)	6(4 to 9)	7(6 to 9)	6(4 to 8)	6(4 to 7)	7(5 to 8)	10.2	39.4	50.4	INCONCLUSIVE	
		Delphi	5(4 to 7)	6(4 to 9)	4(3 to 8)	7(4 to 9)	5(4 to 7)	6(3 to 7)	5(4 to 7)	18.4	45.9	35.7	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#30 Include a plan for systematically training and contacting local site personnel to ensure that they understand the content and importance of collecting PRO data. Ideally coordinated by a lead data manager who monitors PRO completion rates in real time and communicates with sites if completion rates are suboptimal.	**Primary**	**Stakeholder**	8(6 to 9)	7(6 to 9)	8(5 to 9)	7(5 to 9)	7(5 to 8)	7(5 to 9)	7(5 to 9)	6.6	33.1	60.3	INCONCLUSIVE	
		Delphi	8(7 to 9)	7(5 to 9)	7(4 to 8)	6(4 to 9)	7(4 to 8)	8(6 to 9)	7(5 to 9)	12.2	25.5	62.2	INCONCLUSIVE	
	Secondary	**Stakeholder**	7(6 to 8)	6(4 to 7)	7(5 to 9)	7(4 to 7)	6(4 to 8)	6(5 to 8)	6(5 to 7)	12.5	41.9	45.6	INCONCLUSIVE	
		Delphi	8(6 to 9)	6(4 to 8)	5(4 to 8)	5(3 to 8)	5(3 to 7)	7(4 to 9)	6(4 to 8)	16.3	36.7	46.9	INCONCLUSIVE	

Section 10 Methods: Plans to Avoid/Minimise Missing Data

Table 10.1 Responses to items#31 to items#34 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#31 Specify procedures for data collection and management methods to minimise missing data. E.g. checking completed PROMs (including who will check forms and how will they deal with missing PROMs or missing items)	**Primary**	**Stakeholder**	8(6 to 8)	8(6 to 9)	9(7 to 9)	8(7 to 9)	8(7 to 9)	8(7 to 9)	8(7 to 9)	3.0	20.9	76.1	INCLUDE	
		Delphi	8(7 to 9)	8(6 to 9)	7(6 to 8)	7(6 to 9)	8(7 to 9)	7(5 to 9)	8(6 to 9)	6.1	22.2	71.7	INCLUDE	
	Secondary	**Stakeholder**	6(6 to 7)	7(6 to 9)	8(7 to 9)	7(5 to 8)	7(5 to 9)	7(6 to 9)	7(6 to 9)	5.3	35.3	59.4	INCONCLUSIVE	
		Delphi	8(6 to 9)	8(5 to 9)	6(4 to 8)	7(4 to 8)	7(5 to 8)	7(4 to 8)	7(5 to 9)	8.1	35.4	56.6	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#32 Include guidance on discussing importance of PROs with patient	**Primary**	**Stakeholder**	9(7 to 9)	6(4 to 8)	6(4 to 9)	6(4 to 8)	6(4 to 8)	6(5 to 7)	6(4 to 8)	14.9	40.3	44.8	INCONCLUSIVE	
		Delphi	9(8 to 9)	6(4 to 8)	6(3 to 8)	6(3 to 8)	7(3 to 8)	7(6 to 9)	7(4 to 8)	20.2	28.3	51.5	INCONCLUSIVE	
	Secondary	**Stakeholder**	8(6 to 8)	5(3 to 7)	4(4 to 6)	6(3 to 7)	5(4 to 7)	5(4 to 7)	5(4 to 7)	23.0	48.1	28.9	INCONCLUSIVE	
		Delphi	8(6 to 9)	5(3 to 7)	5(2 to 6)	5(2 to 7)	5(3 to 7)	6(3 to 9)	5(3 to 7)	30.3	33.3	36.4	INCONCLUSIVE	
ITEM#33 Establish process for PRO assessment at (and beyond) withdrawal for patients who withdraw early from a study or who go 'off-study'/'off treatment'	**Primary**	**Stakeholder**	8(6 to 9)	7(6 to 9)	6(5 to 9)	8(6 to 9)	8(6 to 9)	9(6 to 9)	7(6 to 9)	7.4	27.9	64.7	INCONCLUSIVE	
		Delphi	8(7 to 9)	7(6 to 9)	8(7 to 9)	9(7 to 9)	8(5 to 9)	7(6 to 9)	8(6 to 9)	5.1	20.2	74.7	INCLUDE	
	Secondary	**Stakeholder**	7(6 to 8)	6(5 to 8)	5(4 to 9)	6(5 to 8)	7(4 to 8)	7(6 to 9)	6(5 to 8)	12.5	39.7	47.8	INCONCLUSIVE	
		Delphi	6(5 to 8)	6(5 to 8)	7(4 to 9)	8(6 to 9)	7(5 to 8)	6(4 to 9)	7(5 to 8)	9.1	38.4	52.5	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#34 Specify that a named person/position at each centre (and/or centrally) be nominated to take responsibility for administration, collection and checking of PROM - specify whether this is or is not the treating clinician	**Primary**	**Stakeholder**	7(5 to 9)	7(5 to 8)	7(4 to 9)	6(3 to 7)	6(5 to 8)	6(4 to 8)	6(5 to 8)	17.2	35.1	47.8	INCONCLUSIVE	
		Delphi	7(7 to 9)	7(4 to 9)	5(3 to 7)	6(5 to 7)	6(4 to 8)	6(5 to 7)	6(5 to 8)	15.2	35.4	49.5	INCONCLUSIVE	
	Secondary	**Stakeholder**	7(5 to 7)	6(3 to 7)	6(4 to 9)	5(3 to 7)	6(4 to 7)	6(4 to 8)	6(4 to 7)	22.4	40.3	37.3	INCONCLUSIVE	
		Delphi	7(6 to 9)	6(4 to 9)	5(3 to 7)	6(2 to 7)	5(4 to 6)	4(3 to 6)	6(3 to 7)	25.3	39.4	35.4	INCONCLUSIVE	

Section 11 PRO-Specific Quality Assurance

Table 11.1 Responses to item#35 to item#38 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#35 Specify how an electronic PRO system/database will be maintained and how investigator will meet regulatory requirements and ensure data integrity and security	**Primary**	**Stakeholder**	7(4 to 8)	7(6 to 9)	6(4 to 9)	8(6 to 9)	7(6 to 9)	7(7 to 9)	7(6 to 9)	8.3	29.3	62.4	INCONCLUSIVE	
		Delphi	9(7 to 9)	7(4 to 9)	5(1 to 7)	8(5 to 9)	7(6 to 8)	7(5 to 9)	7(5 to 9)	13.1	27.3	59.6	INCONCLUSIVE	
	Secondary	**Stakeholder**	6(4 to 7)	7(5 to 8)	6(4 to 7)	7(6 to 9)	6(4 to 7)	7(6 to 9)	7(5 to 8)	12.9	36.4	50.8	INCONCLUSIVE	
		Delphi	8(7 to 9)	7(4 to 9)	5(1 to 7)	7(4 to 8)	6(5 to 7)	7(5 to 8)	7(4 to 8)	15.5	34.0	50.5	INCONCLUSIVE	
ITEM#36 Specify plan to monitor PRO compliance, including adherence to time windows	**Primary**	**Stakeholder**	7(5 to 9)	7(5 to 9)	6(4 to 8)	7(5 to 9)	7(5 to 8)	7(6 to 9)	7(5 to 9)	7.5	38.1	54.5	INCONCLUSIVE	
		Delphi	8(6 to 9)	7(5 to 9)	7(6 to 8)	7(6 to 9)	7(6 to 8)	7(5 to 9)	7(6 to 8)	7.1	32.3	60.6	INCONCLUSIVE	
	Secondary	**Stakeholder**	6(5 to 8)	6(4 to 8)	6(4 to 7)	6(4 to 8)	6(4 to 7)	6(5 to 8)	6(4 to 8)	15.0	44.4	40.6	INCONCLUSIVE	
		Delphi	7(6 to 9)	7(4 to 9)	6(5 to 7)	7(4 to 8)	6(5 to 7)	5(4 to 7)	6(5 to 7)	12.1	45.5	42.4	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#37 Include an overview of PRO administration (data collection), and data handling/transmission and storage procedures	**Primary**	**Stakeholder**	7(4 to 8)	7(5 to 9)	7(5 to 9)	7(6 to 9)	5(4 to 8)	6(5 to 8)	7(5 to 9)	9.3	38.8	51.9	INCONCLUSIVE	
		Delphi	8(6 to 9)	6(5 to 9)	5(5 to 7)	7(5 to 9)	7(5 to 8)	6(3 to 7)	7(5 to 8)	14.1	35.4	50.5	INCONCLUSIVE	
	Secondary	**Stakeholder**	6(4 to 7)	6(4 to 8)	7(5 to 8)	7(5 to 9)	5(3 to 7)	6(5 to 8)	6(4 to 8)	16.0	42.7	41.2	INCONCLUSIVE	
		Delphi	7(5 to 9)	6(5 to 8)	5(5 to 6)	7(4 to 8)	6(5 to 7)	5(3 to 6)	6(4 to 7)	21.2	43.4	35.4	INCONCLUSIVE	
ITEM#38 Ensure plans for administration of PROM(s) are consistent with each PROM's user manual	**Primary**	**Stakeholder**	8(5 to 9)	7(6 to 9)	8(5 to 9)	7(6 to 9)	6(4 to 9)	6(5 to 9)	7(5 to 9)	10.4	32.8	56.7	INCONCLUSIVE	
		Delphi	8(6 to 9)	6(5 to 9)	6(5 to 7)	5(2 to 9)	7(5 to 9)	7(4 to 9)	6(5 to 9)	14.3	36.7	49.0	INCONCLUSIVE	
	Secondary	**Stakeholder**	7(5 to 8)	7(5 to 8)	7(5 to 9)	7(3 to 9)	6(3 to 8)	6(5 to 9)	7(5 to 9)	15.3	35.1	49.6	INCONCLUSIVE	
		Delphi	8(6 to 9)	6(5 to 9)	6(5 to 7)	5(2 to 9)	6(4 to 9)	6(4 to 7)	6(4 to 8)	15.3	42.9	41.8	INCONCLUSIVE	

Section 12 PRO Statistical Analysis

Table 12.1 Responses to item#39 to item# 51 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#39 Include an a priori description of all planned PRO analyses pertaining to the study hypotheses	**Primary**	**Stakeholder**	7(4 to 8)	8(7 to 9)	8(6 to 9)	8(7 to 9)	9(7 to 9)	8(6 to 9)	8(7 to 9)	3.0	18.8	78.2	INCLUDE	
		Delphi	6(5 to 9)	9(8 to 9)	9(5 to 9)	9(8 to 9)	9(8 to 9)	8(7 to 9)	9(7 to 9)	6.2	11.3	82.5	INCLUDE	
	Secondary	**Stakeholder**	6(4 to 6)	6(5 to 8)	7(4 to 9)	7(5 to 9)	7(5 to 8)	6(6 to 8)	6(5 to 8)	6.8	44.4	48.9	INCONCLUSIVE	
		Delphi	6(4 to 6)	7(5 to 9)	6(4 to 7)	7(6 to 9)	8(5 to 9)	7(4 to 9)	7(5 to 9)	11.2	36.7	52.0	INCONCLUSIVE	
Item#40 State the assumptions of PRO analyses	**Primary**	**Stakeholder**	7(7 to 9)	7(6 to 8)	7(6 to 9)	7(5 to 9)	8(6 to 9)	8(7 to 9)	7(6 to 9)	7.6	26.1	66.2	INCONCLUSIVE	
		Delphi	7(6 to 9)	7(5 to 9)	5(3 to 7)	9(6 to 9)	7(5 to 9)	7(5 to 9)	7(5 to 9)	10.4	30.2	59.4	INCONCLUSIVE	
	Secondary	**Stakeholder**	6(6 to 7)	6(4 to 7)	7(5 to 9)	6(5 to 8)	6(4 to 8)	7(6 to 8)	6(5 to7)	12.3	46.2	41.5	INCONCLUSIVE	
		Delphi	7(5 to 8)	5(4 to 9)	5(2 to 7)	7(6 to 9)	5(4 to 7)	6(4 to 7)	6(4 to 7)	14.6	45.8	39.6	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#41 State the anticipated response rate and implications for the sample size	**Primary**	**Stakeholder**	6(5 to 8)	8(6 to 9)	8(6 to 9)	8(6 to 9)	8(7 to 9)	8(7 to 9)	8(6 to 9)	3.0	26.3	70.7	INCLUDE	
		Delphi	7(6 to 8)	8(7 to 9)	9(7 to 9)	9(7 to 9)	8(7 to 9)	7(7 to 9)	8(7 to 9)	4.2	18.8	77.1	INCLUDE	
	Secondary	**Stakeholder**	6(5 to 7)	6 (4 to 7)	6(5 to 7)	6(3 to 6)	5(4 to 8)	6(6 to 8)	6(4 to 7)	15.9	49.7	34.6	INCONCLUSIVE	
		Delphi	6(4 to 8)	6(4 to 8)	6(5 to 7)	6(4 to 9)	5(4 to 8)	6(4 to 7)	6(4 to 7)	19.8	45.8	34.4	INCONCLUSIVE	
ITEM#42 Include an a priori estimation of PRO effect size	**Primary**	**Stakeholder**	7(5 to 8)	8 (7 to 9)	7(6 to 9)	8(6 to 9)	9(7 to 9)	8(7 to 9)	8(7 to 9)	4.5	18.9	76.5	INCLUDE	
		Delphi	7(5 to 8)	9(7 to 9)	9(5 to 9)	9(6 to 9)	8(6 to 9)	7(6 to 9)	8(6 to 9)	4.2	24.0	71.9	INCLUDE	
	Secondary	**Stakeholder**	6(5 to 7)	6 (4 to 7)	6(4 to 7)	5(3 to 6)	5(3 to 7)	7(4 to 8)	6(4 to 7)	17.7	48.5	33.8	INCONCLUSIVE	
		Delphi	6(4 to 8)	6(3 to 8)	5(3 to 6)	6(4 to 7)	5(4 to 7)	5(3 to 6)	5(3 to 7)	27.1	45.8	27.1	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#43 Specify intention-to-treat or per-protocol PRO analyses	**Primary**	**Stakeholder**	7(5 to 9)	9(7 to 9)	9(6 to 9)	9(7 to 9)	9(8 to 9)	7(7 to 9)	9(7 to 9)	4.5	11.9	83.6	INCLUDE	
		Delphi	6(5 to 7)	9(7 to 9)	9(7 to 9)	9(7 to 9)	8(7 to 9)	8(7 to 9)	8(7 to 9)	5.3	16.0	78.7	INCLUDE	
	Secondary	**Stakeholder**	6(5 to 8)	7 (5 to 9)	7(5 to 9)	7(5 to 9)	7(5 to 9)	7(6 to 8)	7(5 to 9)	7.5	36.1	56.4	INCONCLUSIVE	
		Delphi	6(4 to 7)	6(4 to 9)	9(4 to 9)	9(6 to 9)	7(6 to 9)	7(5 to 9)	7(5 to 9)	11.6	32.6	55.8	INCONCLUSIVE	
Item#44 Include a priori identified summary statistics (as appropriate)	**Primary**	**Stakeholder**	7(5 to 9)	7(6 to 8)	8(6 to 8)	6(4 to 7)	8(4 to 9)	7(7 to 9)	7(6 to 9)	15.6	23.4	60.9	INCONCLUSIVE	
		Delphi	6(3 to 7)	7(5 to 9)	7(4 to 8)	7(4 to 9)	8(6 to 9)	7(4 to 8)	7(5 to 9)	13.0	30.4	56.5	INCONCLUSIVE	
	Secondary	**Stakeholder**	6(5 to 8)	6(4 to 7)	6(4 to 8)	5(4 to 6)	5(3 to 8)	7(6 to 8)	6(4 to 7)	21.7	41.1	37.2	INCONCLUSIVE	
		Delphi	5(3 to 6)	5(3 to 8)	6(4 to 7)	5(3 to 9)	7(5 to 8)	5(3 to 8)	5(3 to 8)	25.8	40.9	33.3	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#45 Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e acceptable time windows for each PRO assessment timepoint) before the PRO objective is compromised	**Primary**	**Stakeholder**	7(7 to 9)	7(7 to 9)	7(6 to 9)	7(7 to 8)	8(6 to 9)	7(6 to 9)	7(6 to 9)	3.8	21.6	74.6	**INCLUDE**	
		Delphi	7(6 to 8)	7(4 to 8)	7(5 to 8)	7(4 to 9)	6(4 to 8)	7(5 to 8)	7(5 to 8)	10.6	35.1	54.3	**INCONCLUSIVE**	
	Secondary	**Stakeholder**	6(6 to 8)	6(4 to 7)	6(4 to 9)	6(4 to 7)	5(4 to 8)	7(5 to 7)	6(4 to 7)	14.0	45.7	40.3	**INCONCLUSIVE**	
		Delphi	6(4 to 8)	6(4 to 7)	5(3 to 6)	5(3 to 6)	4(3 to 7)	6(4 to 7)	5(4 to 7)	19.1	48.9	31.9	**INCONCLUSIVE**	
ITEM#46 Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from PROM (domain-specific and/or total) and methods for handling missing items, and methodological papers for composite endpoints (e.g. QTWiST)	**Primary**	**Stakeholder**	7(5 to 8)	8(7 to 9)	8(7 to 9)	8(7 to 9)	9(6 to 9)	7(7 to 9)	8(7 to 9)	6.1	18.0	75.9	**INCLUDE**	
		Delphi	6(5 to 7)	9(8 to 9)	9(6 to 9)	9(6 to 9)	8(7 to 9)	7(6 to 9)	8(7 to 9)	4.2	17.9	77.9	**INCLUDE**	
	Secondary	**Stakeholder**	6(5 to 7)	7(5 to 9)	7(5 to 9)	7(5 to 8)	6(4 to 9)	7(6 to 9)	7(5 to 9)	10.6	38.6	50.8	**INCONCLUSIVE**	
		Delphi	6(4 to 7)	8(5 to 9)	6(5 to 8)	6(5 to 9)	7(4 to 9)	7(4 to 9)	6(5 to 9)	11.5	39.6	49.0	**INCONCLUSIVE**	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#47 State statistical significance levels and include plans for multiplicity/controlling type 1 error.	**Primary**	**Stakeholder**	7(5 to 8)	9(7 to 9)	8(7 to 9)	7(6 to 9)	9(8 to 9)	9(7 to 9)	9(7 to 9)	3.9	14.7	81.4	**INCLUDE**	
		Delphi	7(5 to 8)	9(8 to 9)	9(7 to 9)	9(8 to 9)	9(8 to 9)	8(7 to 9)	9(7 to 9)	4.2	12.5	83.3	**INCLUDE**	
	Secondary	**Stakeholder**	6(5 to 7)	6 (5 to 8)	7(6 to 8)	6(5 to 9)	6(4 to 9)	6(6 to 7)	6(5 to 8)	10.7	43.5	45.8	**INCONCLUSIVE**	
		Delphi	6(5 to 8)	7(5 to 9)	7(5 to 9)	7(6 to 9)	8(5 to 9)	5(5 to 8)	7(5 to 9)	11.6	36.8	51.6	**INCONCLUSIVE**	
ITEM#48 Pre-specify sequence of testing/exploratory analyses to control for multiplicity or pre-specify domains (e.g. in a regulatory trial/labelling claim)	**Primary**	**Stakeholder**	7(3 to 8)	7(6 to 9)	8(6 to 9)	7(6 to 9)	7(6 to 9)	8(6 to 9)	7 (6 to 9)	5.3	28.2	66.4	**INCONCLUSIVE**	
		Delphi	6(5 to 7)	8(6 to 9)	7(4 to 9)	9(6 to 9)	8(4 to 9)	7(4 to 9)	7(5 to 9)	13.7	22.1	64.2	**INCONCLUSIVE**	
	Secondary	**Stakeholder**	6(3 to 7)	6(4 to 7)	6(4 to 8)	5(5 to 9)	5(4 to 7)	6(6 to 8)	6(4 to 7)	15.4	50.8	33.8	**INCONCLUSIVE**	
		Delphi	5(4 to 7)	6(3 to 7)	5(3 to 7)	6(4 to 9)	7(4 to 9)	5(4 to 8)	6(4 to 8)	22.6	39.8	37.6	**INCONCLUSIVE**	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#49 Specify the criteria for clinical significance (e.g. state minimal [clinical] important difference and/or responder definition (size and duration of benefit)	**Primary**	**Stakeholder**	7(2 to 9)	8(7 to 9)	9(7 to 9)	8(7 to 9)	9(7 to 9)	8(8 to 9)	8(7 to 9)	4.5	12.1	83.3	**INCLUDE**	
		Delphi	7(5 to 8)	9(8 to 9)	9(7 to 9)	9(7 to 9)	9(6 to 9)	8(7 to 9)	9(7 to 9)	3.1	12.4	84.5	**INCLUDE**	
	Secondary	**Stakeholder**	7(2 to 7)	7(5 to 9)	7(6 to 9)	7(5 to 8)	6(4 to 8)	7(6 to 9)	7(5 to 8)	9.2	35.9	55.0	**INCONCLUSIVE**	
		Delphi	6(4 to 8)	8(5 to 8)	5(4 to 9)	7(6 to 9)	7(4 to 8)	7(5 to 9)	7(5 to 9)	14.4	35.1	50.5	**INCONCLUSIVE**	
ITEM#50 State how missing data will be described	**Primary**	**Stakeholder**	8(7 to 9)	8(7 to 9)	8(6 to 9)	7(5 to 9)	9(7 to 9)	8(6 to 9)	8(7 to 9)	3.0	20.3	76.7	**INCLUDE**	
		Delphi	7(4 to 9)	9(7 to 9)	9(6 to 9)	7(4 to 9)	8(8 to 9)	8(7 to 9)	8(6 to 9)	6.3	20.8	72.9	**INCLUDE**	
	Secondary	**Stakeholder**	7(6 to 8)	7(5 to 8)	7(5 to 9)	5(5 to 8)	7(5 to 8)	7(6 to 9)	7(5 to 8)	7.6	39.7	52.7	**INCONCLUSIVE**	
		Delphi	7(4 to 9)	8(4 to 9)	7(4 to 9)	6(4 to 8)	7(5 to 9)	6(5 to 9)	7(5 to 9)	12.4	36.1	51.5	**INCONCLUSIVE**	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#51 Describe method for handling missing assessments (e.g. approach to imputation and sensitivity analyses)	**Primary**	**Stakeholder**	6(6 to 8)	8(7 to 9)	8(6 to 9)	7(6 to 9)	9(7 to 9)	8(6 to 9)	8(7 to 9)	3.0	21.8	75.2	**INCLUDE**	
		Delphi	7(5 to 9)	9(7 to 9)	9(8 to 9)	9(6 to 9)	9(8 to 9)	8(6 to 9)	9(7 to 9)	5.1	16.3	78.6	**INCLUDE**	
	Secondary	**Stakeholder**	6(5 to 6)	7(5 to 8)	6(5 to 9)	6(5 to 8)	7(5 to 8)	6(5 to 8)	6(5 to 8)	7.5	45.1	47.4	**INCONCLUSIVE**	
		Delphi	6(4 to 8)	7(4 to 9)	7(4 to 9)	7(5 to 9)	8(5 to 9)	6(5 to 8)	7(5 to 9)	11.2	34.7	54.1	**INCONCLUSIVE**	

Section 13 PRO Data Monitoring/PRO Alerts

Table 13.1 Responses to item#52 to item#53 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting: ≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#52 Describe the role of the Data Monitoring Committee and Quality Assurance for PROs	**Primary**	**Stakeholder**	7(6 to 9)	7(5 to 8)	6(5 to 9)	7(6 to 9)	7(5 to 9)	7(5 to 9)	7(5 to 9)	8.3	32.6	59.1	INCONCLUSIVE	
		Delphi	8(6 to 9)	8(6 to 8)	6(4 to 8)	7(4 to 9)	7(3 to 8)	7(6 to 9)	7(6 to 8)	12.6	25.3	62.1	INCONCLUSIVE	
	Secondary	**Stakeholder**	6(6 to 8)	5(4 to 7)	5(4 to 9)	5(4 to 7)	6(5 to 7)	6(5 to 8)	5(4 to 7)	14.8	53.9	31.3	INCONCLUSIVE	
		Delphi	7(6 to 9)	6(4 to 6)	4(3 to 6)	4(3 to 5)	5(3 to 7)	7(5 to 7)	5(4 to 7)	21.1	46.3	32.6	INCONCLUSIVE	
ITEM#53 Include an a priori plan for consistent/standardised management of PRO alerts	**Primary**	**Stakeholder**	8(8 to 9)	7(5 to 9)	7(4 to 9)	7(5 to 9)	7(5 to 8)	7(5 to 9)	7(5 to 9)	9.1	28.8	62.1	INCONCLUSIVE	
		Delphi	8(7 to 9)	8(5 to 9)	7(4 to 8)	7(7 to 9)	8(5 to 8)	8(7 to 9)	8(6 to 9)	8.6	22.6	68.8	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting:* ***≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'***				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
(symptoms reported by patients that exceed a pre-defined level of severity) to be clearly communicated to all appropriate trial staff	**Secondary**	**Stakeholder**	8(7 to 8)	6(5 to 7)	7(4 to 8)	6(4 to 9)	6(4 to 7)	7(5 to 9)	6(5 to 8)	13.7	38.9	47.3	INCONCLUSIVE	
		Delphi	8(6 to 9)	6(3 to 9)	5(4 to 7)	7(6 to 7)	6(4 to 7)	8(5 to 9)	7(4 to 9)	15.1	31.2	53.8	INCONCLUSIVE	

Section 14 PRO-Specific Consent Information/Confidentiality/Dissemination

Table 14.1 Responses to item#54 to item#56 including overall, summated and individual scores

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting:* *≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#54 Describe informed consent procedure for PRO assessment.	**Primary**	**Stakeholder**	8(7 to 9)	7(6 to 9)	8(5 to 9)	8(5 to 9)	8(4 to 9)	8(6 to 9)	8(5 to 9)	12.8	18.0	69.4	INCONCLUSIVE	
		Delphi	8(7 to 9)	8(7 to 9)	7(4 to 9)	7(6 to 9)	8(5 to 9)	6(4 to 9)	8(5 to 9)	13.7	15.8	70.5	INCLUDE	
	Secondary	**Stakeholder**	8(7 to 8)	7(4 to 9)	7(3 to 9)	8(4 to 9)	8(4 to 9)	8(5 to 9)	7(5 to 9)	17.3	25.6	57.1	INCONCLUSIVE	
		Delphi	8(7 to 9)	8(5 o 9)	6(4 to 9)	7(6 o 9)	7(5 o 9)	5(4 to 8)	7(5 to 9)	14.7	25.3	60.0	INCONCLUSIVE	

			INDIVIDUAL STAKEHOLDER GROUP MEDIAN SCORES (IQR)						OVERALL MEDIAN (IQR)	CURRENT INCLUSION OF CANDIDATE ITEMS BASED ON STAKEHOLDER DATA *Rule for Inclusion of Items in Consensus Meeting:* *≥ 70% rated as 'Critical' AND ≤ 15% rated as 'Not Important'*				DELPHI ROUND 1
Candidate Item	**PRO as primary or secondary outcome**	**Survey Group**	**Patient Reps**	**Researchers**	**Clinicians**	**Methodologists**	**Analysts**	**Reviewers**	**All Stakeholders**	**Rating by % of stakeholders**			**Current Item Level Decision**	**Your Score**
										Not Important [1-3]	**Important [4-6]**	**Critical [7-9]**		
ITEM#55 Specify whether PRO forms will be used to influence therapy or patient management (i.e. will the clinician use PRO responses to inform the patient's care?). State the assumptions of PRO analyses	**Primary**	**Stakeholder**	9(7 to 9)	8(7 to 9)	8(7 to 9)	8(6 to 9)	8(5 to 9)	9(7 to 9)	8(6 to9)	7.6	19.1	73.3	**INCLUDE**	
		Delphi	9(8 to 9)	9(7 to 9)	7(6 to 8)	7(6 to 9)	8(5 to 9)	9(7 to 9)	8(7 to 9)	6.2	16.5	77.3	**INCLUDE**	
	Secondary	**Stakeholder**	8(7 to 8)	7(5 to 8)	7(5 to 9)	7(4 to 9)	7(4 to 9)	9(6 to 9)	7(5 to 9)	12.0	31.6	56.4	**INCONCLUSIVE**	
		Delphi	9(7 to 9)	8(6 to 9)	6(5 to 7)	6(3 to 9)	7(5 to 9)	9(6 to 9)	7(5 to 9)	9.4	26.0	64.6	**INCONCLUSIVE**	
ITEM#56 Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.	**Primary**	**Stakeholder**	9(7 to 9)	6(3 to 7)	5(3 to 6)	5(3 to 6)	5(4 to 6)	5(4 to 7)	5(4 to 7)	24.6	46.9	28.5	**INCONCLUSIVE**	
		Delphi	8(7 to 9)	6(4 to 7)	5(1 to 6)	5(2 to 8)	6(4 to 7)	6(5 to 7)	6(4 to 7)	21.6	37.1	41.2	**INCONCLUSIVE**	
	Secondary	**Stakeholder**	8(7 to 8)	5(2 to 6)	5(3 to 6)	4(2 to 6)	4(3 to 6)	5(4 to 6)	5(3 to 6)	36.6	42.0	21.4	**INCONCLUSIVE**	
		Delphi	8(7 to 9)	4(2 to 7)	4(1 to 5)	4(1 to 8)	4(3 to 6)	5(3 to 7)	5(3 to 7)	34.0	35.1	30.9	**INCONCLUSIVE**	

Section 15 Other Trial Documentation

Table 15.1 Stakeholder Suggestions for items to be include in other trial guidance, training or information materials outside of the trial protocol

Item#	Do you feel any of the candidate items should be routinely included in other trial guidance/training/information materials outside of the trial protocol? If so, please indicate below. [you may choose multiple options per row if you wish]					
		Guidance/training for trial staff % (n)	Information/guidance for study participants % (n)	Statistical Analysis Plan % (n)	Other trial documentation % (n)	Total no of Individual responses
Item #1	List personnel responsible for PRO components of trial protocol.	63.7% (86)	20.7% (28)	10.4% (14)	5.2% (7)	135
Item #2	Describe what is currently known about PROs in this area and explain the gaps in literature.	37.2% (42)	31.9% (36)	23.0% (26)	8.0% (9)	113
Item #3	Provide a rationale for the inclusion of PROs as appropriate to the study population, intervention, context, objectives and setting.	41.3% (57)	28.3% (39)	25.4% (35)	5.1% (7)	138
Item #4	State the PRO study objective in relation to PRO domain/s, patient population and timeframe.	36.9% (55)	24.2% (36)	34.2% (51)	4.7% (7)	149
Item #5	State the PRO hypothesis and corresponding null hypothesis and to which outcome(s) the hypothesis relates.	24.8% (30)	9.9% (12)	61.2% (74)	4.1% (5)	121
Item #6	If PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the sampling method.	38.5% (52)	10.4% (14)	47.4% (64)	3.7% (5)	135
Item #7	State the inclusion/exclusion criteria for PRO endpoint(s) (e.g., language/reading requirements).	49.0% (75)	26.1% (40)	22.9% (35)	2.0% (3)	153
Item #8	Specify if PRO completion is pre-randomisation eligibility requirement.	45.5% (71)	25.0% (39)	26.9% (42)	2.6% (4)	156
Item #9	Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint.	34.0% (53)	13.5% (21)	49.4% (77)	3.2% (5)	156
Item #10	Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom.	32.0% (40)	14.4% (18)	48.0% (60)	5.6% (7)	125
Item #11	Specify the timepoint(s) for PRO analysis (including the principle timepoint of interest) and provide the rationale for these.	39.9% (69)	18.5% (32)	37.6% (65)	4.0% (7)	173
Item #12	Include PRO assessments in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment.	51.4% (74)	22.2% (32)	24.3% (35)	2.1% (3)	144
Item #13	Specify if baseline PRO assessment should be completed before randomisation.	53.5% (83)	20.0% (31)	23.9% (37)	2.6% (4)	155
Item #14	Specify the targeted time and acceptable time windows for each PRO assessment.	50.9% (84)	20.0% (33)	25.5% (42)	3.6% (6)	165
Item #15	If PROs are to be completed in the clinic: specify timing of PROM delivery in relation to clinical assessments (e.g.	60.8% (90)	26.4% (39)	8.8% (13)	4.1% (6)	148

	before/whilst/after seeing clinician and/or clinical assessments).					
Item #16	Justify the timing of PRO assessments. Scheduled PRO assessments should link to research questions, hypotheses, length of recall, disease/treatment natural history, planned analysis and time of comparison must be comparable for both arms.	46.4% (45)	13.4% (13)	33.0% (32)	7.2% (7)	97
Item #17	If PRO is the primary endpoint, state the required PRO sample size, otherwise discuss the power of the PRO analyses.	24.4% (31)	8.7% (11)	66.1% (84)	0.8% (1)	127
Item #18	Describe the PROMs including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, acceptability, recall period. Provide references as appropriate.	36.4% (40)	10.0% (11)	45.5% (50)	8.2% (9)	110
Item #19	Justify choice of PROM(s) by linking specific domains/items to clinical justifications and hypotheses.	41.1% (39)	17.9% (17)	36.8% (35)	4.2% (4)	95
Item #20	Provide evidence of measurement equivalence across modes (i.e., when mixing modes of PRO data collection) and/or of cross cultural validity where different language versions of questionnaires are used.	31.9% (29)	11.0% (10)	46.2% (42)	11.0% (10)	91
Item #21	Outline plans for evaluation of measurement properties, if appropriate (e.g. if not previously validated in the population of interest).	25.8% (25)	8.2% (8)	59.8% (58)	6.2% (6)	97
Item #22	Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population.	51.0% (75)	35.4% (52)	10.9% (16)	2.7% (4)	147
Item #23	Include a pre-specified data collection plan.	49.5% (53)	13.1% (14)	30.8% (33)	6.5% (7)	107
Item #24	Specify how PROM will be completed (e.g. pencil and paper, online, etc).	50.0% (86)	38.4% (66)	7.6% (13)	4.1% (7)	172
Item #25	Specify where PROM will be completed (e.g. clinic, home, etc).	50.6% (86)	40.6% (69)	6.5% (11)	2.4% (4)	170
Item #26	Where applicable, justify use of proxies (define conditions under which proxy assessment is permissible).	49.0% (77)	31.8% (50)	15.3% (24)	3.8% (6)	157
Item #27	Specify who will administer the PROM (e.g. a physician, nurse, etc).	55.2% (90)	34.4% (56)	7.4% (12)	3.1% (5)	163
Item #28	If it is permissible for another person to help the study participant complete the PROM, describe what type and level of assistance is acceptable.	50.9% (88)	38.7% (67)	6.4% (11)	4.0% (7)	173
Item #29	If more than one PROM will be used, specify whether the order of administration will be standardised or randomised.	57.3% (75)	16.8% (22)	22.9% (30)	3.1% (4)	131
Item #30	Include a plan for systematically training and contacting local site personnel to ensure that they understand the content and importance of collecting PRO data. Ideally coordinated by a lead data manager who monitors PRO completion rates in real time and communicates with sites if completion rates are	72.6% (82)	9.7% (11)	13.3% (15)	4.4% (5)	113

	suboptimal.					
Item #31	Specify procedures for data collection and management methods to minimise missing data. E.g. checking completed PROMs (including who will check forms and how will they deal with missing PROMs or missing items).	71.9% (82)	5.3% (6)	18.4% (21)	4.4% (5)	114
Item #32	Include guidance on discussing importance of PROs with patient.	66.1% (82)	25.8% (32)	3.2% (4)	4.8% (6)	124
Item #33	Establish process for PRO assessment at (and beyond) withdrawal for patients who withdraw early from a study or who go 'off-study'/'off treatment'.	56.3% (76)	18.5% (25)	19.3% (26)	5.9% (8)	135
Item #34	Specify that a named person/position at each centre (and/or centrally) be nominated to take responsibility for administration, collection and checking of PROM - specify whether this is or is not the treating clinician.	68.1% (81)	20.2% (24)	9.2% (11)	2.5% (3)	119
Item #35	Specify how an electronic PRO system/database will be maintained and how investigator will meet regulatory requirements and ensure data integrity and security.	56.8% (63)	17.1% (19)	14.4% (16)	11.7% (13)	111
Item #36	Specify plan to monitor PRO compliance, including adherence to time windows.	63.7% (72)	9.7% (11)	16.8% (19)	9.7% (11)	113
Item #37	Include an overview of PRO administration (data collection), and data handling/transmission and storage procedures.	57.9% (73)	12.7% (16)	19.0% (24)	10.3% (13)	126
Item #38	Ensure plans for administration of PROM(s) are consistent with each PROM's user manual.	65.3% (62)	7.4% (7)	17.9% (17)	9.5% (9)	95
Item #39	Include an a priori description of all planned PRO analyses pertaining to the study hypotheses.	20.7% (25)	5.8% (7)	71.1% (86)	2.5% (3)	121
Item #40	State the assumptions of PRO analyses.	21.3% (26)	9.0% (11)	68.9% (84)	0.8% (1)	122
Item #41	State the anticipated response rate and implications for the sample size.	20.3% (24)	8.5% (10)	69.5% (82)	1.7% (2)	118
Item #42	Include an a priori estimation of PRO effect size.	16.0% (17)	7.5% (8)	74.5% (79)	1.9% (2)	106
Item #43	Specify intention-to-treat or per-protocol PRO analyses.	18.7% (23)	8.1% (10)	72.4% (89)	0.8% (1)	123
Item #44	Include a priori identified summary statistics (as appropriate).	16.2% (17)	4.8% (5)	76.2% (80)	2.9% (3)	105
Item #45	Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e acceptable time windows for each PRO assessment timepoint) before the PRO objective is compromised.	28.6% (34)	9.2% (11)	59.7% (71)	2.5% (3)	119
Item #46	Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from PROM (domain-specific and/or total) and methods for handling missing items,and methodological papers for composite endpoints (e.g. QTWiST).	18.5% (22)	5.0% (6)	73.1% (87)	3.4% (4)	119
Item #47	State statistical significance levels and include plans for multiplicity/controlling type 1 error.	15.8% (19)	4.2% (5)	78.3% (94)	1.7% (2)	120

Item #48	Pre-specify sequence of testing/exploratory analyses to control for multiplicity or pre-specify domains (e.g. in a regulatory trial/labelling claim).	15.7% (17)	6.5% (7)	76.9% (83)	0.9% (1)	108
Item #49	Specify the criteria for clinical significance (e.g. state minimal [clinical] important difference and/or responder definition (size and duration of benefit)).	19.5% (24)	9.8% (12)	68.3% (84)	2.4% (3)	123
Item #50	State how missing data will be described.	16.1% (19)	6.8% (8)	76.3% (90)	0.8% (1)	118
Item #51	Describe method for handling missing assessments (e.g. approach to imputation and sensitivity analyses).	15.7% (19)	6.6% (8)	74.4% (90)	3.3% (4)	121
Item #52	Describe the role of the Data Monitoring Committee and Quality Assurance for PROs.	46.2% (49)	13.2% (14)	28.3% (30)	12.3% (13)	106
Item #53	Include an a priori plan for consistent/standardised management of PRO alerts (symptoms reported by patients that exceed a pre-defined level of severity) to be clearly communicated to all appropriate trial staff.	58.3% (70)	16.7% (20)	15.8% (19)	9.2% (11)	120
Item #54	Describe informed consent procedure for PRO assessment.	54.4% (86)	36.1% (57)	7.0% (11)	2.5% (4)	158
Item #55	Specify whether PRO forms will be used to influence therapy or patient management (i.e. will the clinician use PRO responses to inform the patient's care?).	50.6% (79)	37.2% (58)	9.6% (15)	2.6% (4)	156
Item #56	Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.	41.2% (61)	45.3% (67)	7.4% (11)	6.1% (9)	148
					Answered	113
					No response	26

Table 15.2 Delphi Panel Suggestions for items to be include in other trial guidance, training or information materials outside of the trial protocol

Item#	Do you feel any of the candidate items should be routinely included in other trial guidance/training/information materials outside of the trial protocol? If so, please indicate below. [you may choose multiple options per row if you wish]					
		Guidance/training for trial staff % (n)	Information/guidance for study participants % (n)	Statistical Analysis Plan % (n)	Other trial documentation % (n)	Total no of Individual responses
Item #1	List personnel responsible for PRO components of trial protocol.	68.3% (71)	21.2% (22)	7.7% (8)	2.9% (3)	104
Item #2	Describe what is currently known about PROs in this area and explain the gaps in literature.	48.3% (42)	29.9% (26)	17.2% (15)	4.6% (4)	87
Item #3	Provide a rationale for the inclusion of PROs as appropriate to the study population, intervention, context, objectives and setting.	52.9% (54)	30.4% (31)	14.7% (15)	2.0% (2)	102
Item #4	State the PRO study objective in relation to PRO domain/s, patient population and timeframe.	42.3% (44)	23.1% (24)	32.7% (34)	1.9% (2)	104
Item #5	State the PRO hypothesis and corresponding null hypothesis and to which outcome(s) the hypothesis relates.	37.5% (36)	6.3% (6)	56.3% (54)	0.0% (0)	96
Item #6	If PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the sampling method.	44.6% (45)	5.0% (5)	48.5% (49)	2.0% (2)	101
Item #7	State the inclusion/exclusion criteria for PRO endpoint(s) (e.g., language/reading requirements).	54.1% (60)	20.7% (23)	23.4% (26)	1.8% (2)	111
Item #8	Specify if PRO completion is pre-randomisation eligibility requirement.	55.3% (63)	14.9% (17)	28.9% (33)	0.9% (1)	114
Item #9	Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint.	39.8% (45)	14.2% (16)	46.0% (52)	0.0% (0)	113
Item #10	Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom.	45.5% (40)	11.4% (10)	43.2% (38)	0.0% (0)	88
Item #11	Specify the timepoint(s) for PRO analysis (including the principle timepoint of interest) and provide the rationale for these.	43.2% (51)	15.3% (18)	41.5% (49)	0.0% (0)	118
Item #12	Include PRO assessments in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment.	51.5% (53)	13.6% (14)	33.0% (34)	1.9% (2)	103

Item #13	Specify if baseline PRO assessment should be completed before randomisation.	55.5% (61)	12.7% (14)	30.9% (34)	0.9% (1)	110
Item #14	Specify the targeted time and acceptable time windows for each PRO assessment.	51.7% (62)	14.2% (17)	33.3% (40)	0.8% (1)	120
Item #15	If PROs are to be completed in the clinic: specify timing of PROM delivery in relation to clinical assessments (e.g. before/whilst/after seeing clinician and/or clinical assessments).	58.5% (69)	28.0% (33)	11.9% (14)	1.7% (2)	118
Item #16	Justify the timing of PRO assessments. Scheduled PRO assessments should link to research questions, hypotheses, length of recall, disease/treatment natural history, planned analysis and time of comparison must be comparable for both arms.	54.9% (45)	12.2% (10)	32.9% (27)	0.0% (0)	82
Item #17	If PRO is the primary endpoint, state the required PRO sample size, otherwise discuss the power of the PRO analyses.	28.6% (26)	3.3% (3)	68.1% (62)	0.0% (0)	91
Item #18	Describe the PROMs including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, acceptability, recall period. Provide references as appropriate.	43.2% (38)	6.8% (6)	48.9% (43)	1.1% (1)	88
Item #19	Justify choice of PROM(s) by linking specific domains/items to clinical justifications and hypotheses.	48.5% (33)	7.4% (5)	39.7% (27)	4.4% (3)	68
Item #20	Provide evidence of measurement equivalence across modes (i.e., when mixing modes of PRO data collection) and/or of cross cultural validity where different language versions of questionnaires are used.	42.2% (27)	3.1% (2)	53.1% (34)	1.6% (1)	64
Item #21	Outline plans for evaluation of measurement properties, if appropriate (e.g. if not previously validated in the population of interest).	31.1% (23)	4.1% (3)	62.2% (46)	2.7% (2)	74
Item #22	Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population.	55.9% (62)	36.0% (40)	6.3% (7)	1.8% (2)	111
Item #23	Include a pre-specified data collection plan.	51.1% (46)	6.7% (6)	38.9% (35)	3.3% (3)	90
Item #24	Specify how PROM will be completed (e.g. pencil and paper, online, etc).	49.3% (70)	39.4% (56)	9.9% (14)	1.4% (2)	142

Item #25	Specify where PROM will be completed (e.g. clinic, home, etc).	50.0% (71)	41.5% (59)	6.3% (9)	2.1% (3)	142
Item #26	Where applicable, justify use of proxies (define conditions under which proxy assessment is permissible).	50.0% (57)	33.3% (38)	14.9% (17)	1.8% (2)	114
Item #27	Specify who will administer the PROM (e.g. a physician, nurse, etc).	60.2% (74)	31.7% (39)	6.5% (8)	1.6% (2)	123
Item #28	If it is permissible for another person to help the study participant complete the PROM, describe what type and level of assistance is acceptable.	51.1% (70)	38.7% (53)	7.3% (10)	2.9% (4)	137
Item #29	If more than one PROM will be used, specify whether the order of administration will be standardised or randomised.	56.3% (58)	11.7% (12)	31.1% (32)	1.0% (1)	103
Item #30	Include a plan for systematically training and contacting local site personnel to ensure that they understand the content and importance of collecting PRO data. Ideally coordinated by a lead data manager who monitors PRO completion rates in real time and communicates with sites if completion rates are suboptimal.	82.4% (70)	4.7% (4)	8.2% (7)	4.7% (4)	85
Item #31	Specify procedures for data collection and management methods to minimise missing data. E.g. checking completed PROMs (including who will check forms and how will they deal with missing PROMs or missing items).	69.3% (70)	2.0% (2)	24.8% (25)	4.0% (4)	101
Item #32	Include guidance on discussing importance of PROs with patient.	69.3% (70)	24.8% (25)	4.0% (4)	2.0% (2)	101
Item #33	Establish process for PRO assessment at (and beyond) withdrawal for patients who withdraw early from a study or who go 'off-study'/'off treatment'.	56.1% (64)	21.1% (24)	20.2% (23)	2.6% (3)	114
Item #34	Specify that a named person/position at each centre (and/or centrally) be nominated to take responsibility for administration, collection and checking of PROM specify whether this is or is not the treating clinician.	72.8% (67)	16.3% (15)	7.6% (7)	3.3% (3)	92
Item #35	Specify how an electronic PRO system/database will be maintained and how investigator will meet regulatory requirements and ensure data integrity	57.1% (48)	16.7% (14)	20.2% (17)	6.0% (5)	84

	and security.					
Item #36	Specify plan to monitor PRO compliance, including adherence to time windows.	60.5% (52)	11.6% (10)	23.3% (20)	4.7% (4)	86
Item #37	Include an overview of PRO administration (data collection), and data handling/transmission and storage procedures.	63.5% (54)	11.8% (10)	20.0% (17)	4.7% (4)	85
Item #38	Ensure plans for administration of PROM(s) are consistent with each PROM's user manual.	78.9% (45)	3.5% (2)	15.8% (9)	1.8% (1)	57
Item #39	Include an a priori description of all planned PRO analyses pertaining to the study hypotheses.	23.9% (21)	2.3% (2)	73.9% (65)	0.0% (0)	88
Item #40	State the assumptions of PRO analyses.	20.9% (18)	3.5% (3)	75.6% (65)	0.0% (0)	86
Item #41	State the anticipated response rate and implications for the sample size.	20.7% (17)	3.7% (3)	75.6% (62)	0.0% (0)	82
Item #42	Include an a priori estimation of PRO effect size.	16.5% (13)	3.8% (3)	79.7% (63)	0.0% (0)	79
Item #43	Specify intention-to-treat or per-protocol PRO analyses.	20.9% (18)	3.5% (3)	75.6% (65)	0.0% (0)	86
Item #44	Include a priori identified summary statistics (as appropriate).	20.2% (17)	3.6% (3)	76.2% (64)	0.0% (0)	84
Item #45	Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e acceptable time windows for each PRO assessment timepoint) before the PRO objective is compromised.	28.2% (24)	4.7% (4)	67.1% (57)	0.0% (0)	85
Item #46	Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from PROM (domain-specific and/or total) and methods for handling missing items,and methodological papers for composite endpoints (e.g. QTWiST).	24.4% (22)	2.2% (2)	73.3% (66)	0.0% (0)	90
Item #47	State statistical significance levels and include plans for multiplicity/controlling type 1 error.	14.3% (12)	2.4% (2)	83.3% (70)	0.0% (0)	84
Item #48	Pre-specify sequence of testing/exploratory analyses to control for multiplicity or pre-specify domains (e.g. in a regulatory trial/labelling claim).	18.3% (15)	3.7% (3)	78.0% (64)	0.0% (0)	82
Item #49	Specify the criteria for clinical significance (e.g. state minimal [clinical] important difference and/or responder definition (size and duration of benefit)).	18.6% (16)	2.3% (2)	77.9% (67)	1.2% (1)	86

Item #50	State how missing data will be described.	19.3% (16)	2.4% (2)	78.3% (65)	0.0% (0)	83
Item #51	Describe method for handling missing assessments (e.g. approach to imputation and sensitivity analyses).	20.0% (17)	2.4% (2)	77.6% (66)	0.0% (0)	85
Item #52	Describe the role of the Data Monitoring Committee and Quality Assurance for PROs.	50.0% (36)	6.9% (5)	37.5% (27)	5.6% (4)	72
Item #53	Include an a priori plan for consistent/standardised management of PRO alerts (symptoms reported by patients that exceed a pre-defined level of severity) to be clearly communicated to all appropriate trial staff.	61.2% (60)	17.3% (17)	18.4% (18)	3.1% (3)	98
Item #54	Describe informed consent procedure for PRO assessment.	58.4% (66)	39.8% (45)	1.8% (2)	0.0% (0)	113
Item #55	Specify whether PRO forms will be used to influence therapy or patient management (i.e. will the clinician use PRO responses to inform the patient's care?).	50.4% (63)	40.0% (50)	6.4% (8)	3.2% (4)	125
Item #56	Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.	46.2% (54)	46.2% (54)	2.6% (3)	5.1% (6)	117

	Answered	91
	No response	8

Appendix 1 Stakeholder and Delphi Panel Additional Comments

Candidate Item	Stakeholder comments	Delphi Panel Comments
ITEM#1 List personnel responsible for PRO components of trial protocol	• If a very large and complex collaboration a QoL lead for a QoL subgroup of the TMG is helpful • "... responsible for ..." is not clear to me. Is the item about people doing data collection? I would want to know about arrangements for blinding, whether primary or secondary, since a systematic review cannot assess RoB otherwise. But I don't care about who the statistician is ... • For most studies, even if a PRO is a secondary outcome I would rate it as critical. There are, though, a few highly focussed studies which will not directly affect patient factors and we need to recognise these to avoid PROs becoming a barrier to otherwise good research. • I answered this question assuming you meant triallists. If you meant who should complete the PRO, then I would have marked it 9 • Usually, the PRO person is in an advisory function to the clinical team who write the protocol - not really necessary to be specifically listed in the protocol. • Providing a checklist and a list of personnel responsible for PRO components of a trial protocol should enable sites to realize the importance of PRO data just like any other data collected in clinical trials. Ideally these personnel should attend the Investigator Meeting to discuss the rational and importance of the inclusion of PRO in the trial. • I'm not sure what you mean by the responsibilities and by PRO component (choice of outcome? providing instruction?). But if it is about number of people administering the interviews in case of an interview version of a PROM, I would like to have more information. • PRO is important. It could be the secondary outcomes, but it must be included in a trial protocol. • Please rephrase the question been asked here to clarify the criterion being judged. • Where a patient reported outcome is the primary outcome of a trial it is critical to plan who will instruct the patient on the impact as part of the informed consent process and the value of the data being collected. • This is a common source of confusion and needs to be clear to the clinical trial team. With a clear indicator of who is accountable, the trial is far more likely to run smoothly. Without this, various team members can feel as if this "isn't my job" because it is a PRO. • This is critical when a PRO is a secondary outcome because it may not be as intuitive to the study team who often have limited experience with PRO measures. Using the example of how consenting investigator have to be identified in the protocol may be a nice model to consider for PRO measure collection. Accountability is critical to avoid missed time points. • Does this mean who collects the PRO? I think it would be different if administered as an interview, but so often the personnel responsible is just handing over the forms or an iPad or something like that. • If you have qualified people on your team, people that understand measurement, I think the checklist isn't needed or useful. If you have people not trained in assessment, then it could help - maybe.	• Reuse of trial data for meta analyses is a major argument • to me it is more important that PROs included than who included them • Definition of Primary and Secondary would have been useful. Secondary would include input from clinician • For USFDA, primary and secondary outcomes that are part of the testing hierarchy can be in labelling, so our views of evidence information are similar. • As potential REC reviewer the WHO is perhaps less important than reassurance that SOMEONE is committed to following through and knows what they are doing. If included in the protocol changes of staff would require amendments • I find it important that someone responsible is listed, but I consider the listing of a Company or Organisation sufficient • Correct recording of PRO requires training/competence. • The role of personnel must be clarified (e.g. blinded or not?). • In general, I don't see any difference related to the primary vs. secondary "status" of the PRO. An outcome is an outcome and it influences the trial design and statistics. If irrelevant, don't include it in the protocol. • Somewhat vague -- is this asking who is responsible for writing the PRO section in the protocol, or who will be administering/collecting PRO data? • Need to know who to refer questions to. Particularly if trial is a primary outcome. • I think they are both important to publish so people can read and make their own judgements on a personal level • Not sure if you mean "name names," which I think would result in many unnecessary protocol amendments, or "name roles" - such as "trials nurse" or "clinic nurse." The latter would be a 6 for me, the former a 1. It is important that the people who complete this survey know how protocol review is done and what triggers amendments that need to be approved by IRB. • Skill re PRO data collection and analysis is different to other clinical/research skills for cancer trials. Personnel should include patient rep. • I don't think it's important to name the personnel as part of the protocol checklist. • Not sure if this means one person (e.g. PRO trial lead) or all the key personnel administratively responsible. My response assumes the former. • The primary question "how important do you feel it is for .... To be included in a PRO protocol checklist" implies these items are to be considered for the team/personnel implementing the PRO. There are other parties (e.g., funders, academic centres, IRBs, study population, etc.) that have an interest in such design protocol checklists. Thus your assumption should be more clearly stated "for whom" and" to what". I will assume you mean POR research implementers. • If primary outcome, then the protocol writers are responsible; if secondary

		there may be shared responsibility. • I think it is important to identify an individual who takes responsibility for the scientific and methodological PRO details in the protocol - the PRO-go-to person if there are any queries about the protocol (e.g. ethics boards) or during conduct (e.g. queries/clarifications from trial sites). In my experience, typically this would be a trial investigator and member of the trial management committee. Holds whether PRO primary or secondary. • Not 100% clear what is meant by "responsible for". • I haven't previously given much thought (well none) to whether it matters if the PRO is primary or secondary outcome. I can see a case that it should be same for both but my answers will may a bit. • To have a PRO as a secondary outcome is very important as well, I believe it should be in the checklist even if it's an exploratory endpoint which might often be the case. • Listing the personnel is very important to highlight that you need people with PRO skill to be responsible.
ITEM#2 Describe what is currently known about PROs in this area and explain the gaps in literature	• Can reference development work for a trial, would be needed if the study is developing a new PRO • I would expect a protocol to cite the relevant literature about this information and to summarise it - but not to provide details. • you need to be able to justify use of the particular instrument that is used, knowing gaps is part of that • I do think that providing what is known and explaining gaps in the literature would be helpful, however this has to be pragmatic. The checklist should be a checklist and not a massive document that will only put people off from reading it. • This is important to do this work to develop the strategy and for basic background, but not necessarily in a protocol. • Very important information when assessing a protocol. • Same	• Has to be critical as why bother with the project unless there is a known baseline • Justifies time taken by participants to complete the questionnaires. Cogent reason needs to be provided • The discussion of the patient perspective is critical. But the jargon/specialists discussion is not needed here. • This is interesting (I mean: what it is known about the specific PROs adopted), but as a comment of both introduction and discussion. Not critical for the research results. • If it is primary outcome needs to some background explanations. • Brief description - same as for other endpoints • This will help build understanding across all research teams of the overall position/shortcomings re PROs and the need to measure PRO in consistent fashion so that everyone is on the same page. • In primary outcome I think this information is useful to patients and researchers as it provides context. Not so important in secondary outcome. • Process of PRO implementation as secondary outcome should have about the same rigor as for a primary outcome, at least for Marketing Authorization or gaining a claim in SPC • This seems like a very general listing. It's not always necessary to conduct an exhaustive review of all work in PROs in a particular area. You want to be sure that you have the best tool for the job but an extensive review adds costs and time and may not actually help. Especially for a therapy area where measurement is well established and the field extensive. It may be sufficient to review recently published data on PRO instruments to ensure that your selection of instrument is based on the most up-to-date information. • This is a fundamental step in making a sound scientific case for collecting PRO data, as this will consume considerable trial resources and patient effort. Holds whether PRO primary or secondary.

		• This would go into the PRO evidence dossier for submission to my agency for review. Not necessarily in the clinical trial protocol. • It is always valuable to have this information, but it is critical to ensure all information needed to properly implement the protocol and protect the wellbeing of study participants is clearly described and that the effort of be comprehensive in describing background information does not interfere with ensuring the protocol procedures are properly implemented.
ITEM#3 Provide a rationale for the inclusion of PROs as appropriate to the study population, intervention, context, objectives and setting.	• Should be a given • You need to be able to justify use of the particular instrument that is used • As above, I do believe this is important; however it should be concise and not overly long. Providing the rational is very important. • It is difficult to score the secondary outcome question as this is dependent on the phase of the trial. In the phase 2 setting it would be a 4 or 5. In a phase 3 setting the score would be 5 or 6. • Even as a secondary outcome, PROs may be critical part of benefit risk evaluation of an application for marketing authorization of a medicine. • These questions are horrible.	• because many people in the medical community still have mixed or even indifferent feelings re PROs I think this would be helpful • Surely this is another way of asking the previous question - a robust justification is required • Justification absolutely needed from both a scientific and an ethical perspectives • I would consider it more important to include a rationale if no PROs are included in the study • The outcome is a determinant of the trial design and statistics. The very reason for the study (the research question) must be clear a priori. • as above • Same point as above, if you have to provide rationale then it makes you look at the other literature and show how your approach compares • Helpful for primary outcome but not necessary for secondary... • Process of PRO implementation as secondary outcome should have about the same rigor as for a primary outcome, at least for Marketing Authorization or gaining a claim in SPC • PROs as secondary endpoints consume just as much trial resources and patient efforts as if PROs primary endpoint, so justification is just as important, perhaps slightly less critical. • This would go into the PRO evidence dossier for submission to the regulatory agency for review. Not necessarily in the clinical trial protocol. • A difficult statement to unpick. • Is it the rationale for PROs in general or for the specific PROs chosen, or both? • Don't know how to answer this! • This is very important - to not just use what have been used before off the shelves - and could e.g. be supported by a conceptual model. • Study participants should not be expected to complete PRO assessments that are not well considered, justified for their condition and the study. • This is key, without a scientifically robust and relevant objective(s) with clearly defined rationale of the key parameters to be studied, the subsequent methodology and interpretation will be potentially flawed and it will become challenging to draw conclusions
ITEM#4 State the PRO study objective in relation to PRO domain/s, patient population and timeframe.	• Overlaps with previous item #3 - need to be careful not to overload protocol with too much information regarding secondary outcomes. • In context • Not clear what this statement means- multiple interpretations possible. • I am assuming this is to do with defining the "O" if the PICO research question. This is critical because a reader can't assess selective reporting the	• When QOL is a secondary outcome (or even primary) it may be exploratory with regard to domains - whilst I think a QOL objective is essential, it may be difficult to satisfy the criterion as currently worded in some cases. • As above • Consistently with #3 • Importance is equivalent to importance of

	reported results otherwise. • The endpoint model and conceptual framework are essential components of any clinical trial development program. • Again, this is critically important in the formulation of hypotheses to be tested. Having these clear objectives will enable sponsors, ethics committees and anyone involved in the development of protocols to have a greater understanding of the value of PRO data. • Is this your conceptual model (target population, construct of interest)? Unclear wording! • Too much detail may not be applicable for all study designs, especially when PROs are measured as a secondary outcome.	stating the objective in relation to domains/populations/timeframes for any outcome in the study. • See above. The outcome is a determinant of the trial design and statistics. The very reason for the study (the research question) must be clear a priori. • Already captured in main SPIRIT checklist • as above • If PRO study objective not explained fully then it appears to be less important/of lower status to other outcome e.g. survival. When there should be parity. • I think this is critical to primary outcome and important and helpful for secondary outcome • Process of PRO implementation as secondary outcome should have about the same rigor as for a primary outcome, at least for Marketing Authorization or gaining a claim in SPC • Also rather complex. I see timeframe as part of the definition of outcome. • Study objectives should be stated always of course. If PRO is a primary outcome then I presume the objective will relate to possible influence of intervention on that PRO. Is a PRO study objective different from a study objective therefore? • Sorry - I'm not sure how to answer this one either. • I don't understand this item - my experience is that the PROs in RCTs in Pharma are part of the main study so I'm not sure what is meant by the PRO study objective. • Clear hypotheses for primary or secondary PRO endpoints should specify domains, population and time point for assessment of the endpoint.
ITEM#5 State the PRO hypothesis and corresponding null hypothesis and to which outcome(s) the hypothesis relates.	• I'm not clear why a specific null hypothesis is needed, if the general research question and study objectives contain an adequate formulation of the primary and secondary outcomes and how they will be used to assess effectiveness or efficacy. I think his is too rigid and will contribute to the ever longer protocols we see, of which readers and reviewers are able to absorb less and less. • Stating the Null Hypothesis is not important. • as above • If the PRO is the primary endpoint then there must be both a clinically meaningful hypothesis as well as an expected difference to either a standard of care or a comparator being measured. Only in the development of a PRO or if a PRO is part of an exploratory outcome would this answer be not critical. If it is not important then the investigator team should question whether the inclusion of the PRO in a trial is not superfluous and a waste of the patient's time. • Null hypothesis is not necessary if the hypothesis is mentioned. With secondary outcomes, there are not always hypotheses possible. • There is often more than one secondary outcome in a biomedical study and each do not have a specific study objective or hypothesis. If the PRO is a secondary outcome that is identified as a secondary endpoint, then more context is required (important but not critical - 6). But if a PRO is a secondary outcomes that is 'in a list' of exploratory endpoints, the depth of detail in the protocol may not as critical (not important). This applies to many of the questions in this survey. Might there be value (and more clarity) if "when a PRO is a secondary outcome" is divided into "when its a key secondary endpoint" opposed to "when its an exploratory	• As opposed to objectives (which I think are essential), hypotheses are important but not critical • PROMs might be used to gather exploratory data, in which case there may not be a hypothesis attached to them. • I'm likely not being too helpful here but often the 2ndary outcomes are more patient related and therefore of strong interest to patients • Cannot see why this is necessary at the moment • Not sure there will always be a specific relevant null hypothesis • If adequate background information is provided and research objectives stated it is not necessary to explicitly formulate the hypotheses. • This is likely to preoccupy statisticians - I am not convinced • Same • For all of these questions, rather than primary and secondary outcomes, I think the real discrimination here is between statistically tested and exploratory outcomes • I would rather see the alternative hypothesis than the null hypothesis as it is more informative. • This is a general requisite for experimental research. PRO-based research does not represent an exception. • Already captured in main SPIRIT checklist • Seems more relevant for primary

	endpoint"?	outcomes • However, often it is also relevant to allow for analysis of secondary PRO endpoints and more broad descriptive or exploratory analysis of PRO items or scales that are par tot a standard instrument but in the specific trial are not selected to be a primary endpoint. • Certainly stating the hypothesis is critical (particularly for primary endpoints) but stating the null hypothesis? That's what we do as students in stats 101; don't see that for other endpoints in the protocols I read. The null hypothesis is (usually) implied by the motivated hypothesis. • if there is a hypothesis it is crucial to state it but the PRO might be purely descriptive in which case there may not be a hypothesis • Ensures that the data is analysed correctly and, if hypothesis is proved, adds weight to the conclusions • Critical for primary outcome... useful for secondary... • I am not sure about the distinction between issues 3-4-5. Do 3-4-5 go from general objectives to more specific hypothesis? • Process of PRO implementation as secondary outcome should have about the same rigor as for a primary outcome, at least for Marketing Authorization or gaining a claim in SPC • In CONSORT group we have often debated the difference between objectives, aims, and hypotheses, without a satisfactory resolution. • So I'm unsure how this question differs from the preceding one. • I wouldn't refer to null hypothesis. Indeed I don't see an obvious need to request different information for PROs than for outcomes in general, as in main CONSORT. • Yes very important and great to link with potential responder definitions. • The primary endpoints require pre-specification of associated hypotheses and study objectives whether PRO or otherwise. If a PRO is measuring a key secondary outcome, thus should also be linked to hypotheses and considered in determining sample size required to reject the null hypotheses
ITEM#6 If PROs will be collected in a subset of the study population or in specific centres, include a description/rationale for the sampling method.	• Not appropriate for primary outcome • Should always be included • Again, stating it like this increases the likely length of the protocol; it ought to be possible to incorporate a clear idea of the subgroup for whom pros will be collected in the objectives, without a formal extra statement. • Necessary to interpret the applicability of the result for the PRO/subset to the wider trial cohort. • Unlikely then that the PRO will be a primary endpoint if only collected in specific centres/subset of study population • It's essential to make sure the sample matches the PRO • PRO subgroup analyses are currently flawed because it is rarely mentioned in protocols and considered after - subgroups should be defined at the earliest stage of protocol development and included in the statistical analyses plan. • PROs should be PROMs? Sampling method includes sample size calculation (for entire study population), inclusion criteria, selection method etc. • This is critical in order to evaluate the risk of bias. • If a primary outcome is not collected on the full	• not recommended • to me just makes sense to explain why you would do this • Sampling must be robust • This is not realistic when it is the primary end point of the trial • I don't see how this applies to Primary Outcome? • This information is critical for interpretation of findings. • See above. This is a general requisite for research. PRO cannot be a second-class research • methods needs to be clear in both cases • Also important to be clear that this approach does not introduce bias. • Why PRO should ever only be done on a subset? To maximise PRO response and robustness, need whole study population. • Clear description is absolutely necessary, but rationale is often obvious from the context (e.g., due to sample size or power considerations) so doesn't need

	study population, then that definitely needs to be explained - also true, but to a lesser extent for significant secondary outcomes.	to be explicitly stated. • Very important to include this in primary outcome... not sure about secondary but feel it would be useful... • A clear and unambiguous description likely more important than a clear rationale • When a PRO is a primary outcome: Not applicable • Process of PRO implementation as secondary outcome should have about the same rigor as for a primary outcome, at least for Marketing Authorization or gaining a claim in SPC • Possibility of selection bias can be a critical flaw, so this item is critical, regardless of whether PRO primary or secondary. • Method might imply something like a 20% random sample, but one might also decide to do this in only some centres, which is still a subset. The latter isn't really what I think of as a "method". • Yes, need description of course. Rationale is something else - would be nice to know why, also linked to whether the subsample is large enough to provide useful results. • This situation is not logical for a primary endpoint. I cannot envision a study where the primary outcome does not apply to all participants.
ITEM#7 State the inclusion/exclusion criteria for PRO endpoint(s) (e.g., language/reading requirements).	• Should be included when considering the overall trial inclusion and exclusion criteria - cannot really be separate unless for a specific (non-representative) sub study. • I think it is unwise to have different inclusions/exclusions for the patients on whom outcomes will be measured, in contrast to the patients who will be excluded from the trial itself. • If the primary outcome, then I would expect this to be described in when defining the trial populations. • Depends on the availability of an interviewer administered version • I remember having a discussion with an oncologist about this. A PRO was the secondary endpoint in a breast cancer study and I was asked at an Investigator meeting if a participant was unable to read/write would that exclude them from the study? I think we have to be sensible about these things and in exceptional cases allow patients to participate if they cannot complete a PRO by themselves. I suggested that as long as it was noted that the PRO was completed in an interview format that would be okay. • I would expect these to be the same as for the overall trial, if they are *not* for some reason, than the rationale and special criterial need to be clear. • This is critical in order to evaluate the risk of bias.	• This may be a general requirement. • this is important as I assume it will then let the researchers assess from an equity standpoint • Patients are not always white middle class especially but not exclusively in the Midlands • only if they differ from general eligibility requirements • This is important to state overtly to ensure confidence in results. This requirement should be equivalent in importance to any language/reading level-sensitive information presented to the patient, including informed consent materials. Alternate methods for data collection, e.g., staff presenting information or items orally to accommodate literacy challenges, must also be stated. • See above. These are general requirement for research endpoints, no matter whether biomedical or psycho/behavioural • as above • Robustness of conclusions could be undermined if study excludes disadvantaged groups • Process of PRO implementation as secondary outcome should have about the same rigor as for a primary outcome, at least for Marketing Authorization or gaining a claim in SPC • Surely inclusion is defined implicitly by eligibility for the trial plus the info in previous item. • • In the stated example, one would then exclude those with inadequate skills. • • These terms also caused problems - so we adopted eligibility rather than inclusion and exclusion in main checklist.
ITEM#8 Specify if PRO completion is a pre-randomisation eligibility requirement.	• As above • Is captured in eligibility criteria (SPIRIT) anyways • I feel I am answering the question of whether pre-Rx PRO completion should be a requirement, rather	• I would think it would have to be if you didn't want bias - and again, this would clarify re equity (or help to) • Not sure I completely understand the

	than whether this should be SPECIFIED. • Depends on the SoA and frequency of completion, e.g., daily diary vs. monthly assessment • a must because it may mean a larger sample size and you need to account for more missing data if you don't address this issue • As above - we need to be sensible about PRO data completion - if it is not captured then the risk to reliability and robustness of results is a definite worry. • ? unclear question • I believe that the PRO completion (irrespective of whether the PRO is a primary or secondary outcome) should be used in pre-randomization as a gatekeeper with respect to assess whether the patient adequately comprehends the PRO. The investigator team should be concerned with respect to having chosen a PRO with a concept of interest if a patient at the early stages of the trial cannot complete the PRO. • In order to evaluate the external validity of the study. • Rating would be higher if a specific score were an eligibility requirement, not just whether it was completed.	point. Are you saying patients have to be willing to complete PROs to be randomized -- or that patients cannot be randomized until they have completed the PRO? I could support the former, not the latter. • I would be concerned here that people are not excluded from participation because they are unable or unwilling to complete PRO questionnaires. I realise that this is not quite what you are asking but it may be an implication of how such a requirement becomes interpreted. This is potentially coercive • This should hold true whether the assessment is via patient-report or via other information capture. • Eligibility requirements must be always specified. PRO are not an exception • All aspects of adherence to follow-up are an eligibility requirement • as above • I think that PRO completion pre-randomisation should be an eligibility requirement for all such studies and this should not be an "if" but rather trial designers should be told: "List PRO completion pre-randomisation as an eligibility criterion." • Not sure I understand the question. • If a patient has to do a PRO to be eligible for a study would this be ethical? • Rather baseline (pre-treatment) than pre-randomisation. • This is a good strategy to reduce missing data at baseline - critical when PRO is primary outcome and good practice when PRO is secondary. • In principle this info is covered by existing item.
ITEM#9 Identify the PRO endpoint as the primary, secondary (and if so - whether a key/important secondary), or an exploratory endpoint.	• Only use a PRO if it meets the objectives of the study, PRO outcomes may be collected and then not analysed which is potentially unethical and a waste of resources. Also need to avoid multiple testing/fishing exercises. • I don't agree that there should be grades of secondary outcomes! This imposes a lot of extra information demands on PRO protocols that, to my knowledge are not part of non PRO trials. • This is part of any guidance on protocol writing. The question is more about the distinction btw secondary and exploratory endpoints based on allocation of alpha (type I error control) • Question does not make sense if we are asked to rate PRO as a primary or secondary outcome • this is SOP for a protocol • From a regulatory perspective this is crucial. If this is not mentioned in the protocol then it will not be likely to even consider a label claim. Also for the analyses it will be critically important. • This is a confusing question. Primary outcome = primary endpoint!? • This is often omitted and causes confusion for study managers when trying to determine the level of linguistic validation required for the study. • This is critical, in order understand the study objectives and the proposed sample size, as well as inform the statistical analysis plan.	• For secondary outcomes I think this is particularly important. It should be stated up front the role the PRO plays as a secondary outcome. Based on this, I might alter my responses to Q1-8 as if exploratory, I may not feel that indicating the details of the PRO as a secondary endpoint as critical (although I would still find them very important) • Assumes that secondary is after primary in time frame • speaks to justification • Again, I don't see any difference with respect to general requirements of endpoint definitions in clinical trials. • Already captured in main SPIRIT checklist • as above • Might need further clarifying language for this one about whether we are talking about within the PRO endpoints only, or within the larger hierarchy including other clinical trial endpoints. When PROs are a separate sub study, I often specify primary, secondary, and exploratory endpoints within the PROs only. Also, this is only ONE way to handle multiplicity. It is possible to include an alternate methodology which would not require specification of a hierarchy of endpoints. • Really important in both to identify this info • Not clear how to deal with this when some protocols include 2 or 3 "primary" outcomes • This is linked to 3-4-5. • no-brainer • This is important for industry/product

		development trials, but probably less important for other trials, e.g., CER.
ITEM#10 Describe the PRO constructs used to evaluate the intervention e.g. overall QOL, specific domain, specific symptom.	• See comments for #9 • If you are demanding reporting of underlying constructs, you re also demanding that a theory and full validation of the PRO exists and is described. Would it not be simpler to reference the published work which supports validity of the PRO, rather than include a lengthy description? • Would advocate that the domains be described (Alcohol use) but not the specific questionnaire (AUDIT vs. CAGE). This would allow the protocol team to explore which specific questionnaires to use without having to modify the protocol if different questionnaires are selected than originally envisioned. • most clinical teams won't know what that means but it also explains why so many PRO analyses are done poorly/wrong and results are ambiguous - therefore important in an effort to fix the underlying problem • Although describing constructs in the protocol is important I do think that there is a risk of the checklist being too long and folk will not read it! • Always!!! • From own experience in the field I know that the constructs to be measured are most times insufficiently described. E.g. if the construct QoL is measured, authors often only state the used the SF-36 and cite the inaugoratory article. However, critical reflection on the definition used in the inaugoratory article is lacking - but is maybe not fitting the PRO constructs as defined by the authors which use the SF-36 for their research question. We have highlighted this issue in a paper which has been recently published: Lange, T., Rataj, E., Kopkow, C., Lützner, J., Günther, K.-P., & Schmitt, J. Outcome Assessment in Total Knee Arthroplasty: A Systematic Review and Critical Appraisal. The Journal of Arthroplasty. doi:http://dx.doi.org/10.1016/j.arth.2016.09.014 • I believe this is not important if the PRO is validated at the item/symptom level and being used in the appropriate population. If only a part is being used for hypothesis testing of an instrument modification in a phase 2 setting this is more important. • If exploratory, this could be done in the SAP instead of the protocol.	• just so everyone is on the same page • Yes but don't close eyes to unexpected findings • This question is ambiguous - does it mean --- Describe the PRO constructs themselves? Or list which constructs are use? IF the first - for primary (score = 5), for secondary (score = 3). If the second, then for primary (score = 9) and secondary (score = 9) because these are required for hypotheses and objective statements. • Measurement is meaningless if the construct being measured is not clearly identified in advance. Constructs assessed via patient report are particularly vulnerable to messiness of conceptualization, but this requirement should apply to all measures in a trial. • Important but not critical. The "meaning" of the PRO (i.e. which is the latent variable they are supposed to represent/reflect) may be a matter of interpretation (it is an inference). The reader is free to disagree with the Author. Also, from the reader's perspective, the PRO may be self-explaining. • Already captured in main SPIRIT checklist • Important to describe this, but I would not prescribe the level of detail in a checklist. • Readers of any published paper with PRO data need to be able to look further into the data so need to understand the constructs • not clear how this differs from a clear hypothesis specifying domains • A description does not seem necessary. Identification and justification of specific domains should already be covered by 3-4-5. • Process of PRO implementation as secondary outcome should have about the same rigor as for a primary outcome, at least for Marketing Authorization or gaining a claim in SPC • If a PRO is a secondary outcome, the specific domains of interest for inclusion as secondary outcomes should be listed. Depending upon the hypothesis, some domains may be included as exploratory endpoints only. It may also be desirable to list specific domains higher in the hierarchy than others, • This is a major trap if 'HRQoL' only is specified, as it is so vague, rarely explicitly defined, and multi-dimensional. If secondary, only 'not important' if exploratory. • Need enough info for same method to be implemented by others. • very important - good to do e.g. using a conceptual framework • Assumes PRO secondary is a key outcome
ITEM#11 Specify the time point(s) for PRO analysis (including the principle time point of interest) and provide the rationale for these.	• The PICOT statement usually represents the T as timing. Isn't this already assumed? Or is this PRO SPIRIT guideline incorporating the existing general SPIRIT guideline? • Am confused. These questions are just separating components that have already been asked about. • These points are all really intuitive and should be essential for any outcome measures used in a clinical trial • typically in the protocol and specifics in the SAP • Please spell principal right (not principle!) • The timing should coincide with the maximum	• I think it's critical to state the time point, and important but not critical to state the rationale for the time point. • Speaks to justification and ensures consistency across sites - assuming that the administration matches the time point in question • Again: mandatory specifications for any outcome/endpoints variable. No exception for PRO • Already captured in main SPIRIT checklist

	anticipated effect of the intervention on PRO.	• You mean "principal," not "principle." • PRO time points must relate to known likely trajectory of illness/recovery. No point in measuring QoL re continence (for example) only up to 1 year, if it is known that continence peaks at 3-4 years (for example). • Time points should be clearly specified. I do not often include rational for the time points because they are often based on a complex combination of reasons and discussions by multiple committees. • with a secondary endpoint there may or may not be enough previous literature to be clear on precise time point • This is unclear. Rationale is covered by 3-4-5 and timing covered by 14. This seems to imply that there will be time points where PRO is collected but not analysed? • Process of PRO implementation as secondary outcome should have about the same rigor as for a primary outcome, at least for Marketing Authorization or gaining a claim in SPC • Another trap - the 'right' PROs (clinically relevant) assessed at the 'wrong' (missing all the key 'action') times can lead to misleading conclusions - which is a waste of all the PRO data collection and analysis effort. • In general I'm not too keen on expecting to know rationale for all choices. • What is the principle time point? Do you mean interim analysis here before database lock? • Very important to include time points for both data collection and analysis of course. • For secondary this could be deferred until SAP but should be prespecified
ITEM#12 Include PRO assessments in the main protocol schedule of assessments, specifying which PRO measures (PROMs) will be used at each assessment	• List clearly on Schedule of Events table with footnotes as needed. • It will facilitate the assessment of the protocol, but if it is not in the table it can be retrieved from the protocol text. • I would specify the time points at which PRO is done and the broad domains (e.g. Alcohol use), but not necessarily the specific questionnaire (e.g., AUDIT) in case the protocol team decides a different measure is a better fit for the population while operationalizing the study (e.g., CAGE) • If the PRO assessment schedule is not included then there will be much confusion and ultimately the data will suffer. Very important to have the correct data at the right time! • Patient burden could be significant depending on the number of measures being used in the study. • For secondary outcomes, an appendix could be acceptable.	• This item seems to also answer 13 and 14. So, practically this may be sufficient on a checklist. • Essential part of the methodology • see above comment • A separate PRO checklist is not necessary for this and many of the points here. These are principles of good measurement and good trial practice that are no more or less applicable to patient-reported measures than to other trial measures. • See above. • Already captured in main SPIRIT checklist • For my studies, the test schedule often includes "PRO Booklet" time points but details about which PROs are in each booklet are described elsewhere in the protocol. • This is a key trial map for all concerned, regardless of whether PRO 1ry or 2ry.
ITEM#13 Specify if baseline PRO assessment should be completed before randomisation	• Always! • I do not understand the question; this is not specific to PROs and needs to be described for all assessments whether PRO or not. • For me, "baseline" means pre-Rx - so I don't think this needs to be specified. Rather, I would want to examine carefully any departures from this assumption, i.e. when might data collected after Rx is valid/allowable. • This would be applicable only for open label study. The practicality of requesting a PRO assessment prior to randomization is unknown; the value of comparing data (change from baseline) btw an assessment where pts don't know on which tx they are and an assessment where pts know on which tx they are is introducing variability.	• This item seems very similar to item #12 • I think you have this one previously • See above. • Already captured in main SPIRIT checklist • Per my previous comment, this should be required, not an "if" question. • This is dependent on the set-up of the trial – the trial may have multiple randomizations or a split registration-randomization enrolment procedure. This is also included in 14. • Relevant if completed before treatment, rather than before randomisation • I suspect it might be hard operationally to

	• I think by default any baseline assessments would be completed before randomization. Perhaps it should be stated "specify if baseline PRO assessment should be completed after randomization, with rationale for this timing" • In the context of a clinical trial, a baseline assessment is not an "outcome" of the treatment under study, so I wouldn't use the PRO term for a baseline assessment. • This is critical if you really want to know a 'true' change! • they should specify that the baseline assessment should be done after randomisation • Consider combining with or putting adjacent to item #8 • This is critical for open-label studies, as knowledge of intervention could affect baseline PRO. • similar to previous question	assess PROs pre-randomisation in many contexts. I guess the concern here is whether in an unblinded trial a patient's reporting might be influenced by which treatment they have been assigned to. As I think post-R is the likely default, I don't see it as all that important generally. Of course there may be notable exceptions. • Is it a baseline if this isn't true? • or is this getting at the fact that not all PROs can be assessed at baseline e.g. how much better do you feel
ITEM#14 Specify the targeted time and acceptable time windows for each PRO assessment	• Should apply to all outcomes/visits - not specifically PROs. • I think this was already captured around item #12. • I think that this is carrying he protocol to a level of detail that might be excessive for some trials. • This is better wording than just the "time point" - as in a previous Item#question. • Target time is definitely important; the time windows can go in a Study Manual and need not go in the protocol to allow for change after the protocol is final. • Not necessarily required in protocol - maybe more appropriate in associated trial guidance. • maybe not in a protocol but it needs to be pre-determined somewhere in writing • and how deviations with be reported to the IRB	• critical for meta analyses • I believe it should be clear that the trial has taken into consideration the response window and what will be included for the analysis. • Each stage must be carefully time controlled • Targeted time is critical; time window should be defined at the analysis stage only, not as part of study conduct. • see above 11 & 12 • Targeted time is important, windows less so • see above • The targeted time must be specified. The time windows can be given as a guide, but if the trial personal is in doubt it is better to complete the PRO as the time windows can be reviewed at analysis stage and sensitivity analysis done. • May be very hard to do a priori. Would suggest this be part of analysis. • This is a tough one. Specifying windows can lead to a large number of protocol violations. Also, this can lead site staff to not administer questionnaires if outside the window. I usually try to encourage completion as close to the specified time point as possible, but also encourage completion at next available visit if a time point is missing. Late data is better than no data. On the analysis side, for FDA registration trials, I specify acceptable windows for analysis in the statistical analysis plan. For non-FDA registration trials, I do not prespecify acceptable windows for analysis. • Time is already covered in previous question - windows can be hard to predict with certainty • Time windows may be more loosely defined or specified in technical appendix in secondary endpoint setting. • Timing is a key design issues, regardless of primary/secondary. Time windows help site staff practically and support scientific robustness. • Overlaps previous re targeted time.
ITEM#15 If PROs are to be completed in the clinic: specify timing of PROM delivery in relation to clinical assessments (e.g. before/whilst/after seeing clinician and/or clinical assessments)	• May not be feasible to enforce an order - must be after consent for GCP reasons. • Not necessarily required in protocol - maybe more appropriate in associated trial guidance. • reduce bias • ALL of these are very important. If this is not specified we will not get over the 'car park' effect! • In trials where interventions are planned that may introduce discomfort or potentially even pain this potentially has a major impact on PRO responses. • Timing should be standardized in relation to clinical assessments, and rationale provided for actual	• I feel like this depends on the context of data collection. For example, if it is expected that clinical assessments will be influenced by PRO completion than this is pertinent - if the data is collected for the purposes of research and does not serve as an intervention I might feel less strongly about this point. I would recommend clarifying this point as it would change my response! • important or fear things could be lost/forgotten • as in 14

	timing.	• However the completion of PRO questionnaires should not interfere in the clinical interaction or overburden patients - so this is difficult to answer in the abstract. However if it is not stated such an assessment could not be made by a REC • The necessity for this varies by study. • I find it more important that the study maintain their PRO completion procedure throughout the study. In the case of open Trials (no blinding of patients), equal ways of PRO completion in the Treatment arms are essential, the concrete order of completion/individual assessment is of minor importance to me. • This depends on how related are PRO and other clinical assessments. • This should be evaluated on a case by case basis. In some studies this is critical, in others in may not matter. • Are we now shifting to "PROMs"? This is often a matter of specific clinical situations, clinic organization, etc. I think it should be noted but this is relatively minor. • where timing in relation to a clinical assessment is relevant • As well as options if a primary approach is indicated. • This will be dependent on the trial objective.
ITEM#16 Justify the timing of PRO assessments. Scheduled PRO assessments should link to research questions, hypotheses, length of recall, disease/treatment natural history, planned analysis and time of comparison must be comparable for both arms	• Desirable - but protocol also has to be practicable, not weighted down with details that aren't relevant to the collection of high quality data. • important but probably in the body of the protocol rather than a check list • Might be difficult to schedule if there are many other secondary outcomes. But if PRO is primary outcome it is extremely critical • The question in the survey is asking for a single answer to too many aspects. Critical are research question, hypothesis, planned analysis and time of comparison. Less critical especially for secondary is length of recall and disease/treatment - but this is dependent on the disease under investigation and assuming that it is not a longitudinal trial design over many decades. • This item contains too many issues. It is therefore maybe not so helpful for a checklist. • These points should be "as relevant" and not all inclusive. • Depends on the hypothesis and motivation. There are many reasons why you may only ask a single arm.	• How is this different from Item #11? • see above • While the schedule of PRO assessments should be linked to all of these things, it will be very laborious to write out all this rational in the protocol. • General requirements for clinical trials, whatever the outcomes/endpoints • Awkward wording. 2nd sentence: Isn't the timing always the same for all arms? It says 'both' but trials can have >2 arms • Isn't this the same as the previous checklist item #11? I have a hard time including this info in protocols, because the process to select time points is often quite complex taking into account all the things listed in this items plus others (like planned clinical tests and visits and feedback from multiple committees/reviewers). • Seems redundant with item 12. Also, in some particular circumstances, asynchronous assessments may be an appropriate design. • Aside: This item is complicated! Tone may be too prescriptive. • Not keen on asking for justification. Already asked for rationale. • Very important - which takes a lot of cross-team discussions to achieve. • This is a confusing question -- multiple concepts are included, would split off • This issue is confusing and overlaps other items already covered.
ITEM#17 If PRO is the primary endpoint, state the required PRO sample size, otherwise discuss the power of the PRO analyses	• Uncertain meaning of second question given the main item starts 'If PRO is the primary endpoint ...' • All trials are powered, usually, on their primary outcome. I don't understand why you would have anything different for a PRO trial? • If primary, then I would regard this as essential. If secondary, then I would expect the trial to have more power for the PRO than the primary outcome, so not essential (unless the PRO is only being collected for a subgroup, when the power should be described). • Secondary outcome question not relevant	• Second question is not relevant if the PROM is the primary outcome (as stated in the item) • Not sure I understand the reason for the question on secondary outcome given the main question. • If used for an exploratory objective, perhaps this falls in the important but not critical category for Secondary Outcomes. • I think this is better answered by a methodologist or statistician than a

	• Although question specifies primary endpoint, I think this is equally important for secondary endpoints as well. • When PRO is a Secondary Outcome this is not applicable	patient • I am not a statistician but sampling must be robust and adequate • Since this was specific to PRO as a primary endpoint, I did not answer the second part • For this and other points, need the same methodological rigour for PROs as other endpoints. • It's confusing to answer this item separately for Primary and Secondary Outcome because that's already embedded. I think if the PRO is primary, a sample size justification is required. If the PRO is not primary, discussion of PRO power is important but not critical. • should do power and sample size • As Item #17 specifies "If PRO is the primary endpoint" I have intentionally provided no response to 'When a PRO is a Secondary Outcome'. • no comment if PRO is secondary outcome as that is not the question • See above • Already captured in main SPIRIT checklist • I checked 1 for Secondary Outcome because the item pertains only to primary endpoint. • Sample size should be checked even if PRO is a (key) secondary endpoint • This question only relates to PRO as primary outcome? • This question does not apply to the second row as the question is only for prim endpoints • The way this question is worded, not applicable is really the answer, with respect to PRO as a secondary endpoint
ITEM#18 Describe the PROMs including, number of items/domains, instrument scaling/scoring, reliability, content and construct validity, responsiveness, sensitivity, acceptability, recall period. Provide references as appropriate	• Brief description, Provide refs to avoid information overload. • Lots of detail! Long protocol! • Item not clear to me. Apart from defining the outcome really carefully (which will involve items/domains and time points), I don't think these details need to be in the protocol, just references cited. • This is important information for the publication, not necessarily the protocol. • This is an odd question as we often refer to a core or methods paper around the development and validation of a PRO. Given word limits, this is the preferred option. The info must be available but not constantly duplicated. • Could just include reference to article which does this • All this information is too much for a protocol. A short synopsis is needed. • For the sample of interest only. Many just report ICC etc. for a variety of conditions very rarely the condition being assessed so the stats are meaningless • that may be too much for a protocol - but it should be written down/evaluated somewhere • There should be a description including number of items/domains, instrument scaling/scoring and recall period, and references if available. The other aspects are important background but this information may not be easy to compile for a protocol, and most often is included in a PRO dossier where the properties of the instrument are presented in more detail. I think all of this is too much detail for a protocol. • important to know if the PRO is 'fit-for-purpose' • Again only scored this on the basis this is checklist info- all this detail needs to be documented in the full protocol • Answer made that secondary outcome where PRO will not be used as a label claim in the SmPC.	• Would provide references rather than describe all the detail on responsiveness, sensitivity, acceptability and recall • again, think this is best answered by methodologist but thinking you need this for publication • Essential • The description seems overly detailed for a checklist - suggest requiring the same amount of detail as for other outcomes. • Also provide a copy of the PROMs in protocol appendices • This interests me more in terms of assessing burden re completion • Links or appropriate references might be more appropriate for this as I can imagine this could get pretty lengthy and unwieldy • General requirement of any measures adopted in clinical trials. • PRO must not be conceived as low-level measurements: they must be the best possible given the research questions. • There are too many items in this list - some are important some are not. • If PRO is a secondary outcome, this is still important, but the details can be included as an appendix to the protocol • Some justification is needed but this list is overkill. Do we provide this level of justification for blood pressure? • Not sure how to answer this for secondary. Some of the elements I would rate highly (scoring, validity) whereas others not so (sensitivity, recall period) • If established instruments, description may be covered by references. • Aside: A lot of detail in this item, tone is perhaps too prescriptive.

	• can be referred to other sources • This is frequently best done as an appendix rather than in the body of the protocol because it can be extensive, particularly if it is a new PRO that is not published yet so a simple citation isn't possible. • This information is critical but could be provided as an appendix or hyperlink. • This type of information could be included in an appendix both from the primary and secondary outcomes. • when available • Should be able to just provide the manual.	• This would be described in the PRO evidence dossier for submission to regulatory agency. It does not need to be described. It's unclear to what degree it would need to be in the clinical trial protocol. • PRO has become PROM. Not sure id score all elements as 9 however. • I do not believe it is essential to provide detailed measurement development and validation history for every PRO assessment used in a trial, any more than similar details are required for other instruments used in trials. A basic description of the PRO instrument (should include number of items, simple description of scaling scoring, and an example of the questionnaire should be included, development history and psychometric evidence of appropriateness of the PRO endpoint should be referenced. An appendix to the protocol containing trample PRO with scoring should be included for any PRO in a protocol And if changed during the study, should be provided in revised form in amendments.
ITEM#19 Justify choice of PROM(s) by linking specific domains/items to clinical justifications and hypotheses	• Should have been dealt with in objectives above. • You have asked a very similar question before. • Yes, we often see PROs almost pulled 'off the shelf' simply to show one has been used without much thought as to the most appropriate one. The choice should be as robust as the rest of the methodology. • I think this is important in development of the PRO questionnaires, but don't think it needs to be in the protocol • Helps to clarify the rational for choice of PRO instrument! • If the PRO is used as a primary outcome then it must be assumed that the regulators have approved/recommended this tool for labelling and that the PROM will follow the accepted standard procedure. Where the PROM(s) are secondary and not part of a label claim the justification for testing to avoid a false positive result should be higher.	• As above, but a measure like this might be necessary until PROs accepted as normal practice. • To me this duplicates items above - if the use of PROs is properly justified up front (see earlier questions) this would form part of that justification - or should • Important but not critical. • Again, the PRO/domain link is an inference. The reader is free to accept it or not, but this does not prevent the PRO from being a relevant outcome measure. • But also allow for exploratory/descriptive analysis of the remaining domains, scales or items. This descriptive data provides an overview of patient experiences and is valuable. • This would be described in the PRO evidence dossier for submission to regulatory agency. It does not need to be described. It's unclear to what degree it would need to be in the clinical trial protocol. • Some overlap with previous. seems to come too late • I prefer explain to justify. • Yes very important • Suggest omit clinical justification and focus on Linking PRO to hypotheses. Protocols generally require hypotheses that are clinically justified. Additional justification of the instrument used to test hypotheses in terms of the clinical justification is adding bulk without adding insight. Would this be expected of creatinine assays?
ITEM#20 Provide evidence of measurement equivalence across modes (i.e., when mixing modes of PRO data collection) and/or of cross cultural validity where different language versions of questionnaires are used	• Should be included in relation to inclusion & exclusion criteria, methods of data collection. Again references added as needed. • Be careful not to set the standard so high (in theory) that no-one is brave enough to do these trials. Many of these theoretical problems will not turn out to be problems in practice, and we should carefully weigh up the burden of demanding a standard for which we don't yet have evidence of benefit. • This information might not always be available, but should be mentioned, regardless. • But only citing references. • This is part of a TMF not the protocol • Essential if used in another language • Important in development of the questionnaire, but does not need to go in the protocol	• If the role of the PRO as a secondary measure is to provide evidence of measure equivalence, this should be stated and details included accordingly. • Provide the state and quality of the evidence, but if evidence doesn't exist this limitation could be noted instead. • These seem like important details but only applicable if trials include diverse populations or will be mixing modes of administration. • 9 for the cross cultural validity and different language versions. 5-7 for the different data collection modes. Much more is known about different modes' stability.

	• too much for a protocol, maybe an ops manual • This is also a level of detail that will be difficult to include in a protocol, but does belong in a PRO dossier for submission. Especially the information on cross-cultural validity will be difficult to compile for large trials that may be done in many countries. In many cases the linguistic validation work is not available at the time the protocol is written, but is done in parallel. I think this is too impractical to require. • This is critically important for large international trials and especially when more than one mode of data collection is being used. From an operations perspective sometimes more than one mode of data collection might be used so having this information would be helpful. • Where the PROM(s) are secondary and not part of a label claim the measurement is important to address but from a practical point of view should not be addressed at a level where it impacts the power calculation and a decision on the size of the trial population to be studied. • Or a justification - this doesn't mean extensive testing is always required, but this needs to be addressed sufficiently for the study. • Evidence of cross-cultural validity more important than evidence of equivalence across modes, an assessment of likely equivalence could be sufficient for the latter. • It's important but people rely on qualitative equivalence which is sort of useless when comparing scores. So it's important, but not as it's done.	• don't feel qualified to comment on this - so discount my answer • Post-hoc evidence could be accepted. • Again, some of this more detailed information may be referenced or placed in an appendix • Important issue. Yet, non necessarily this evidence is available. Plausible justifications can substitute for the missing evidence. • I am mindful that this information is not always available- for example for different languages. So it should not be a stringent criterion. • Some mention needed but holding protocols to this level of evidence could stop research in its tracks. • This would be described in the PRO evidence dossier for submission to regulatory agency. It does not need to be described. It's unclear to what degree it would need to be in the clinical trial protocol. • don't know enough to answer this • Yes. I think it is important to highlight here that ePRO validation is from a scientific perspective. ePRO developers sometimes claimed that they have data showing validation but that's from a technical perspective. • Also important to include feasibility in different populations. Some scare away and think older people can't use ePROs for example. • Not important. This is an overblown issue; meta analyses demonstrate that equivalence is generally present across modes. • This is not information required in the protocol. It is important in evaluating the results, but not for ensuring proper implementation of study assessments.
ITEM#21 Outline plans for evaluation of measurement properties, if appropriate (e.g. if not previously validated in the population of interest)	• Should be validated before using in a definitive trial - maybe in a pilot study • If it hasn't been validated in the population, probably shouldn't be using it. • Complicated, multi-part question - with weasel words "if appropriate"! I don't think evaluation of measurement properties should ever be a primary objective of a substantive RCT. So this would be appropriate for a feasibility RCT. • This will be defined in the SAP not in the protocol • This information can be briefly mentioned in the protocol, but the full details should be in the Statistical Analysis Plan rather than the protocol. • Should be a separate SAP. • See comment above, without evaluation in population of interest these results are virtually meaningless • we conduct a full psychometric analysis of trial data outside of the clinical trial CSR • This is a serious omission in many protocols for instruments that do require validation data to be generated from the trial and including this would help to ensure that the appropriate variables are included to enable evaluation of measurement properties with trial data. • Key thing here is the "if" clause - if measures have already been studied in terms of psychometric properties, this is not usually important. • In fact, if the PRO is not validated, it should not be used in a RCT. It should be piloted and validated before!! • Need clarification on this item If the measurement properties of the PRO is unknown, why specific this as a primary endpoint in an intervention study • The change from baseline in PRO that is clinically important must be pre-specified.	• Measure must be validated prior to use in trial • If the role of the PRO as a secondary measure includes plans for eval/measurement etc. this should be stated and details included accordingly. • irrelevant to most protocols • This is not part of the trial but a side study, unless a new PRO is used that is validated alongside the trial. That is not realistic when the PRO is the primary endpoint. • Really if it hasn't been validated in that population I would say do not have as the primary outcome! • if PRO primary endpoint, measurement properties should have been determined before the trial • speaks to justification • Ensuring that measures are appropriate and credible is a necessity. If those data cannot be cited from prior work the evidence must be evaluated within the trial. • Either the measure is validated or not. Application of PRO should not be mixed, in the same study, with validation of the same PRO. In this sense,my score =1 refers to the "already validated" case: but please consider my comment in evaluating it (better: "non applicable"? • This is additional research (which I highly support) but not part of the primary protocol. • This would be described in the PRO evidence dossier for submission to regulatory agency. It does not need to be

	• If the primary endpoint is related to the psychometric properties of the measure, this is relevant. • Basic measurement properties in that sample should be reported EVEN IF they have previously been validated in that sample.	described. It's unclear to what degree it would need to be in the clinical trial protocol. • Is a PRO endpoint does not have proper evaluation of measurement properties, it would not be included to support a primary endpoints • Is "if planned" better? • important to highlight WHEN this is planned i.e. before pivotal studies • this is outside the scope of a trial protocol • Only for studies where validation of PRO is an objective. Otherwise this is information more appropriate to an SAP
ITEM#22 Specify the estimated time to complete each assessment, and discuss feasibility of assessment for the population	• Very briefly, for practical purposes, but will only be an estimate as participants will vary. • Not in the protocol. Belongs in the PIS and IRAS form • It can be part of the general rationale. • This will be important to avoid drop-outs due to burden of administration. • These are typically details for the REC/IRB to consider. Realistically, I don't think investigators can know in advance how feasible it will be to collect one or more PROs as specified - unless a feasibility trial has been done. • The problem is that those are only estimates not necessarily applicable across the study population • In my experience, an important consideration, but time to complete and feasibility in the population of interest is not often known while the protocol is being written. • Time to complete each assessment not necessarily required in protocol - would be more appropriate in application for ethics and local governance review. • This is typically included in the ICD and the protocol • This is nice to have but not a must have. • Helps to understand the burden on the participant. As researchers we can get carried away by wanting to collect lots of PRO data but when we really think about the burden of spending an hour completing PROs it can help but things in perspective and encourage us to prioritize. • in protocol, not in a checklist • This question is difficult to answer. In my opinion, time to complete is less important than the feasibility of assessment for the population. • If the PRO is validated in a study population it would be used to establish the primary outcome and then the feasibility would have ideally been part of the validation this should then not play such a large role. This should then also hold true for the secondary outcome as long as the secondary outcome is not an exploratory outcome (where this should then be rated higher). • Feasibility of assessment more important than specifying the estimated time to complete.	• I would include (for the primary outcome) if length is a barrier to potential completeness of data, how it might be handled. • I feel this is important to increase usage and convince the folks who aren't sure or aren't using • Needs a significant time allocation but important • speaks to burden - REC needs to know this • This is good practice but the bar for PROs is different from that for other types of measures, and it should not be. This requirement would support the legacy of inappropriate differential treatment of PROs. • Not critical, especially if previous literature is available, • Very brief statement only. • I agree with specifying the time to complete each assessment. I have never discussed feasibility of assessment in a protocol, unless the assessment is very lengthy. • 2 rather different issues • Also important to include feasibility for different modes in different populations. Some scare away and think older people can't use ePROs for example. • This is a double barrelled question • This information should be detailed in site training and manuals. The protocol need only address what in brief. • If measures are extremely brief and/or there or only a few PRO measures, the discussion of feasibility of assessment can be omitted
ITEM#23 Include a pre-specified data collection plan.	• Repeats previous items. • Not sure what this means, and/or how it differs from other points. • Do not understand what is meant here ... • What is this item? How does it differ from a "schedule" (cf previous question)? • Not sure what this means - e.g. whether proxy completion is allowed, etc.? But this is asked in Q26 below.... • Standard in any trial • Would not put in protocol, this is usually a document developed by the Data Management Centre. • Unclear to what this point refers given earlier questions re data collection time points, methods etc. • required by our Protocol SOPs • Not sure what this means, beyond questions that have already been asked about choice of measures, timing of administration, and modes of administration. What other parts of the plan are you thinking about?	• Not entirely sure what a data collection plan entails. • Vague wording - unclear exactly what this item means • If items 24-29 are included, this item could be left off. • Need to control and administer efficiently • I'm not entirely sure what this refers to. The planned timing of assessments? I thought we had earlier? • see above 11 & 12 - to me this is a related issue • Not sure what this means. • General research design requirement • Since this is a protocol checklist, the plan is already 'pre-specified' by definition • I don't know what this checklist item means. Too broad and vague. • not sure what this means • What is meant with data collection plan? • Not sure what a pre-specified data

	• Not completely clear how this is different from question 16 - scheduled PRO - if the research question is addressed with the PRO and the time frame question 4 then the response here must be the same. • Schedule of assessments, mode of administration and the like must all be pre-specified. A separate Data Management Plan can be used for ensuring data quality, data transfers, etc. If you mean mode of administration - that is covered in 24. • This could be included in the statistical analysis plan. • I am a little unclear what is meant by a data collection plan	collection plan is • Many of the criteria already rated reflect a pre-specified data collection plan (eg. timing of PRO collection in relation to clinic visits)
ITEM#24 Specify how PROM will be completed (e.g. pencil and paper, online, etc.).	• Remember to include qualitative measures e.g. focus groups • State broadly (online, interviewer-administered, self-administered, etc.) but not too specifically, such as stating the software to be used for an online questionnaire. • This is definitely critical, a must have. • Answered based on the assumption that the PRO is validated. • These don't need to be in the protocol, could be in a supplementary document addressing details of trial conduct • And what backup approaches are put in place if the approach doesn't work. If plan to administer online but system not available. goal: avoid protocol deviations	• I think this is important to note • Simple statement but without this could be an admin nightmare • more important that HOW is ensuring equality of access - would be looking for this to be included in the justification • Necessary "Methods" description, whatever the measurement type • Very brief mention only • Can be part of appendix for secondary endpoint; not necessarily part of protocol.
ITEM#25 Specify where PROM will be completed (e.g. clinic, home, etc.).	• If settings are relevant to the study question or PROs themselves • Score based on practical issues if the PRO can be performed at home and is lay language friendly and/or patient is trained in completion not as important. • And what backup approaches will be put in place. Plan to administer during appointment but the subject doesn't get to the survey, is home completion with mail return an option? goal: avoid protocol deviations	• I think this is somewhat contingent on what role the PRO plays in the overall study design and how varied the potential processes might be across the design and time points. • Downgraded. It will be a mixture weighted I expect to the clinic • this seems similar to item #15 • This is covered by previous related to timing • This item seems critical to me only if patients have a choice where to complete the forms and if they are not blinded to the Treatment. • Necessary "Methods" description, whatever the measurement type • Very brief mention only • Can be part of appendix for secondary; not necessarily part of protocol.
ITEM#26 Where applicable, justify use of proxies (define conditions under which proxy assessment is permissible).	• Proxy assessment (e.g. of QoL) doesn't correlate well with patient assessment - so it should really be treated as a separate outcome variable. • If there is a use of proxies, then it is not a PRO • Perhaps would go into a study manual, and not the protocol. An example of this would have helped me understand the issue. • Generally we use the term Observer Reported and restrict those observations to countable observations • Highly relevant to paediatric studies. • FDA discourages the use of proxies for these assessments so I hesitate to rate this highly as it should not be encouraged. • if a proxy completes the questionnaire, it is no longer a prom, but an observer-reported outcome measurement instrument • in protocol • If it is relevant to the study question or PROs themselves • Proxies should never be used. If a patient cannot report for themselves (e.g., paediatric or cognitive impairment), then observers or clinicians can be the reporter on an assessment but they should not be asked to assess symptoms or things they cannot know. They can only report on observable things (e.g., Observer-reported outcome or Clinician-reported outcome, NOT proxy-reported outcome). In some cases, a caretaker may have to read the PRO	• irrelevant to most protocols • this item relates to item #15 and #7 • Typically need to clarify if an observer report or self-report. US FDA does not recognize that someone can be a "proxy"; typically a different instrument is needed. • enables equality of access to be assessed • Necessary "Methods" description, whatever the measurement type • It would be helpful to distinguish the type of proxy - is it a family member (as in brain tumours PROMs may be commonly down by carers) or clinicians/research personnel. If aperient in clinic asks for help- is the researcher allowed to help? • This will be applicable only in well-defined special circumstances. This should not be considered a standard practice or something that should be advocated across the board. I'm concerned that putting it as part of a checklist might imply this is a good option. • We typically do this outside of the protocol (in training materials or forms instructions). • Can be part of appendix for secondary;

	items to a patient (e.g., if patient cannot read). In those cases it is critical to provide training to those caretakers that the information/ratings should come only from the patient and the caretaker should do no more than simply read the questions. • This belongs in the protocol AND training materials	not necessarily part of protocol. • Our organization discourages use of proxy report, so this would not be relevant. Not sure proxy completion should be allowed
ITEM#27 Specify who will administer the PROM (e.g. a physician, nurse, etc.).	• Should be the patient!! • This will be in REC application anyhow. • As long as it is in compliance with current legislation we do not need to know the specific person who will administer the PROM • Remember role of experts by experience in collecting data • Specify in protocol only if who administers it is truly important to the PROM, otherwise allow sites some flexibility. • Unclear question. Do you mean in an interview version. Or do you mean that should be specified who is the proxy? Now it seems who is actually completing the prom, which is by definition the patient! • If it is relevant to the study question or PROs themselves, i.e., if the investigators or previous knowledge indicated that this might make a difference in respondent participation or answers • I don't understand this question. Are you asking who should hand the questionnaire or device to the patient? In the case of PRO measures, the patient self-reports, i.e., self-administration. Or, devices are sent home with patients so they do the assessments at home. • This is a very important point - I am not aware of evidence, but assume this will impact on the results • Reply based on the assumption that the patient reported outcome measure is not in response to a physician administering a specific test. If the PROM is dependent on a task given then this is critical. • Could be ePRO or VRS so not specifically administered by anyone. • Not by discipline but instead by role as a study investigator.	This also seems to align with how the PROM is administered? If interview administered this should be covered. think this is very important because patients often give different responses to different health professionals as per 25 above Study staff may change; this item is better suited for the manual of procedures and not required for the checklist for protocol inclusion. A PRO is by definition self-administered. I assume that this question relate to the case where there is no other option and proxy assessment is permissible Surely this will depend on e.g. whether or not completed on line and whether proxies are involved. I suggest clarifying the term "administer." The extent to which it is permissible for the respondent to have support or assistance in PRO completion, and the nature of that support, must be documented. Necessary "Methods" description, whatever the measurement type That really depends on the PROM and how it has been used or validated. Do we mean giving the questionnaire to the participant or act as a proxy? If it is about giving the questionnaire - this may be difficult to specify as it may vary by centre and depends on local organisation of work. Getting into micro-management here We allow sites the flexibility to select the appropriate clinical staff. These folks have a variety of titles, so specifying this in the protocol could lead to inadvertent protocol violations when a site uses different terminology.
ITEM#28 If it is permissible for another person to help the study participant complete the PROM, describe what type and level of assistance is acceptable.	• Difference to item #26 too subtle i.e. revision of wording required • help by reading questions and ticking forms/completing on line form with respondents responses • And, most importantly, whether the "helper" will be blinded to treatment allocation. • Same comment as above • Again difficult and situation specific, don't want to be too proscriptive and find a section - e.g. blind or partially sighted people who need questions reading to them and their answers recording are suddenly excluded because this has not been explicitly allowed. • Could be specific • Not required in protocol - could be in associated guidance. • more for ops manual • This is different from proxy, and it is essential that procedures for any kind of assistance are clearly spelled out. • This is best done in training materials for the sites. • Specific to translation - can an interpreter read and help complete the PROM?	It depends a lot on the client group specific conditions may require more support than others so I think this will need to be consider depending on the clinical group PROM must be self-completed I believe that addressing assistance broadly is important recognizing that different levels/approaches to assisting completion of PROs might exist. This may also be contextual for patient populations. this would be covered in trial induction training instead if you don't you are going to be downgraded by GRADE or whatever Demographic differences would make this important This item overlaps with item #26 part of proxies above - yes include but don't over complicate Necessary "Methods" description, whatever the measurement type I think we have to accept that PROMs - as often reported by patients - will to a certain extent capture the illness perception of the social milieu of the patient (independent of whether there is formal help or not). This is the nature of the measure - with advantages and disadvantages. See above. This will be useful in a SOP, not sure it belongs to the protocol. Getting into micro-management here. Do you want to call out blind people? Those with Parkinson's who can't hold a pen? You do what is appropriate for individual needs and there are many "special circumstances." We typically do this outside of the protocol (in training materials or forms instructions). It would not be appropriate to deviate from the user

		manual for the instrument. Therefore, it is difficult to see how this would be relevant in most cases. This is often termed 'scribing', and clarification of whether a scribe may help the patient complete is important. Also important would be identifying who that scribe can be (i.e. may it be a family member who could potentially shift the patient's responses)?
ITEM#29 If more than one PROM will be used, specify whether the order of administration will be standardised or randomised.	• Depends a bit on what the PROMs are and whether they are likely to influence each other significantly • I fear that introducing all these items on details will make researchers think about it and brings new/stupid ideas that go in the opposite direction of pragmatic trials! However, if a trial really, really wants to mandate the order this needs to specify! • maybe helpful for methodological insight, but not critical and only if there are hypotheses for why order of administration might be important • "...specify the order of administration." • Can be specified in other documents, not important for protocol. • The order should be standardized unless the purpose of the study is to test for order effects. • good point • Standardization is preferred.	• Important as the order may influence responses - • Would aid analysis, and metaanalyses • same reason as above • The specific order of administration is not necessary for inclusion of in the protocol but is a key detail for study staff administering measures and would be important to include in the manual of procedures for the study. • I can see that this matters to the analysis but would need to be convinced that it makes a difference to burden on participants • Importance of this varies by study and measure. If order effects could affect data and their interpretation then they should be called out. • Important. Yet, this depends on the the time intervals between administrations • ..or not specified.... • Order is important and should be standardised. • Small point • Often not stated because this is obvious if using pre-printed booklets or an electronic system. • Logistically challenging to randomise for paper-based PRO collection. • and also the order of the PROMs in relation to other tests e.g. lab test
ITEM#30 Include a plan for systematically training and contacting local site personnel to ensure that they understand the content and importance of collecting PRO data. Ideally coordinated by a lead data manager who monitors PRO completion rates in real time and communicates with sites if completion rates are suboptimal.	• This item is too complex (multi-component) to properly respond to. • depends on experience of using that PROM • Doesn't belong in the protocol. Belongs in Ops manual and associated SOPs / WIs • Important, but belongs in site manuals and trial SOP, not the trial protocol, I think. • No need to put in protocol. Can be covered in a SOP • Too much detail. • This only pertains if the PRO is being administered locally (not by telephone via a central CRO, etc.) • agree important, as impossible to collect these data retrospectively from clinical notes for example • Site initiation issue, as far as I am concerned. Not for the protocol. • Not part of the protocol, part of the IM • This should be done as a general rule for all of the data in the protocol (in accordance with ICH-GCP), not just the PRO data. So no need to specify this for PRO data alone. • Training is needed but is not included in detail in the protocol. This information goes in the investigator manual. • All essential for transparency and duplication in future trials • Not required in protocol - should be included in trial operating procedures conducted by trials unit. • This is part of the Investigator meeting and site initiation process SOPs • ops manual • This is critically important to be conducted, but can be in the study manual/procedural binder, rather than the protocol. • The training and monitoring aspects are important. I am not sure that the lead data manager is the right person for this role however as they are usually not interacting with sites directly. I think the role responsible should be reconsidered. • The training and co-ordination need to plan at the	• I think this is important for data quality - but it seems there are 3 concepts listed here - training of sites; who conducts training; and monitoring PRO completion rates across sites. For a checklist it might be worth separating these topics out? • the induction training is important but doesn't need to be detailed in the protocol • Totally essential • This item dos not apply to self-administered PRO, which is very often the case • not necessarily in protocol • people should understand what they are doing and why • The protocol should state there is a plan, but the plan should not be in the protocol. It should be part of the monitoring procedures, guides etc. • Critically important • I don't traditionally think of this being part of the study protocol, but it is SO important, perhaps it should be in every protocol. • I recognize a plan for training and contacting personnel is important, but feel this does not need to be included in the protocol, hence the low rating • Critical, like for any other measurement in clinical trial. It is atypical task delegated to a Contract Research Organisation. The key point is: PRO make no exception • This goes outside a specific protocol and could serve as an educational note to accompany the checklist. But as part of the protocol? No. • This is handled outside of the protocol document for cooperative group trials.

	start of the trial. Sites that have difficulties with PRO completion should be contacted after the first couple of subjects and closed if the issue persists. The rational being that the data collected by later subjects is biased with respect to the subjects included at the start of the trial, essentially creating two different populations within a trial. • I would put this in data management plans. It is critical for the study to be successful - but not necessarily in the protocol. The checklist needs to be created in sections that indicate which documents need these items • As with item 24 above this information could be in a supplementary document	• Really important that data managers are properly trained to highlight to local staff the importance of data completion. • This is important but typically not in protocol in my experience. Usually a separate document • Depends on the complexity of the protocol. • Belongs in trial conduct documentation, not protocol. Brief mention of value of such training may be useful in the protocol. • This is important but not for the protocol but maybe a site manual • and kick-off, make sure to get the PRO person in on the kick-off and not just the other RCT data collection team • This is operational and does not necessarily belong in a protocol. Also, the plan may need to be adapted over time, and ideally it will not be locked in to a protocol, which restricts necessary flexibility. • This detail is more than would be done for other assessments. Suggest it us more important for training and monitoring, so should be part of study procedures and FAQ manual. • Mechanisms and strategies to reduce the amount of missing data are important, and high completion rates improve the overall integrity of the data and the robustness of the conclusions drawn
ITEM#31Specify procedures for data collection and management methods to minimise missing data. E.g. checking completed PROMs (including who will check forms and how will they deal with missing PROMs or missing items)	• *Again, ops manual, not protocol* • *No need to include in protocol. Can be covered in separate document.* • *If using computer-assisted interviewing techniques, methods to minimize missingness can be automated.* • *an issue that we had when we tried to ask research nurses to screen for non-completed questions and ask respondents if they had been deliberately missed, is that often it is stated that responses will be confidential* • *Just general good practice re validating and checking completeness of data. Not a protocol issue.* • *Part of the IM* • *Important, but does not belong in protocol document* • *Not required in protocol - should be included in trial operating procedures conducted by trials unit.* • *As with item above, these are critical data collection & management SOPs that should exist outside of the study protocol.* • *I'm not sure if this comes later as I did not receive the list attached to my invitation email. However along with this, if electronic mode of data collection is used, then a plan for dealing with device issues needs to be included in the protocol so that sites know how to deal with it up front and they do not default to paper which is not acceptable in most cases. The question is worded for paper PROMs completed at sites but many trials have data collected using diary devices by patients outside the clinic and those situations require a specific approach.* • *I wish this happened more often - there is nothing worse that analysing longitudinal PRO datasets and having lots of missing data! I worry about protocols which do not say how missing data will be dealt with - can create undesirable bias and impact the validity of the results.* • *also when would this check be performed and if patients would be contacted should the* • *Secondary score based on assumption that PRO will not be a label outcome.* • *Belongs in a Data Management Plan* • *Likely to be addressed with error messages for ePRO or VRS*	• usually specify how many times will chase and who will chase • as per 30 • in a similar way to other data collection points in the trial • While important I'm not sure how feasible, will add to cost of implementing PROs in a study and may be prohibitive? • Same as above: procedure should exist and be referenced in the protocol, but does not need to be described in the protocol itself. • Like #30 this is very important, but it usually goes in the site training materials. • General requirement in clinical research protocols. • Already captured in main SPIRIT checklist • In the era of electronic data collection - to specify if an item completion is mandatory or if participants *are allowed to skip items.* • The majority of data in most settings these days are collected online where this is not an issue. It will only become more so in the future. This item is an anachronism. • This is handled outside of the protocol for cooperative group trials. • This is an important and generic protocol for both primary and sec PRO outcomes. • Sometimes in training manual rather than in protocol • Isn't this covered by 23? Should also include collection of reasons for missing data. • Belongs in trial conduct documentation, not protocol. Brief mention of value of such procedures would be useful in the protocol. • Again, important but for a site manual

ITEM#32 Include guidance on discussing importance of PROs with patient	• Important, and reasonable to include in the participant information, but doesn't belong in the trial protocol, I think. • No need to include in protocol. Can be covered in separate document. • Other than general encouragement, I don't see what basis there is for such a discussion. • Part of IM • Not sure this is relevant. Wouldn't the PRO instrument have standardized instructions (written or verbal)? It would not be valid to include additional, protocol-specific guidance. • This information has to be consistent to manage bias • Important, but does not belong in protocol. Include in training materials. • Not required in protocol - should be included in guidance notes provided to site. • This is an ICD issue, and is part of the inclusion criteria • We need to get out of the habit of thinking PROs are just questionnaires - they are powerful tools and we should convey that importance to patients. • This can be helpful to minimize missing data - if patients feel engaged and understand the importance they are more likely to report. • Why? this will not influence the data collection - PRO´s are already included and thus there is no need to discuss this with the patient • Training materials • Patients generally willing to complete PROs. More important to focus on staff training #30 • This is an important aspect for the study team but does it need to be in the protocol? Can some actions go on the checklist but NOT be for protocol inclusion but instead study implementation - Manual of procedures?	• This could be included in a separate document/SOP • I feel like this is an important aspect to include but temper my rating here as this should link to why the PRO is designated as the Primary/Secondary outcome. This would be part of study consent or recruitment? • Not important in terms of approving a clinical trial. • This could be in the participant info sheet • is important to cover in trial induction training • to gain cooperation and complete answers • Communication in simple terms vital • I gave a low rating unless the item has specific clinical relevance • If they are walking away with the PRO, e.g. a daily diary, this is more important than when they are completing them in office. • Non-standardized procedures - such as communication - is to be avoided in a CT Protocol. Rather, we need to give clear instructions to patients regarding when and how PRO will be collected. • Like #30 this is very important, but it usually goes in the site training materials. • This heavily depends on the nature of the PRO. • SO: my intermediate scores reflect a mean of my possible responses. "it depends" would have been a more appropriate answer. • but also include information to the patient of what happens to the PROMs after they complete it- where it goes, who sees it, whether their doctor/nurse will see or not. • Goes well outside the protocol and is part of clinical care. • Extremely important • This is handled outside of the protocol for cooperative group trials. • Again generic protocol of importance in patient education for the purposes of completing PRO. • Belongs in trial conduct documentation, not protocol. Brief mention of value may be useful in the protocol. • Again, important but for a site manual • I think this should be done with the staff as well • Optional • In fact, the guidance on portable of PRO is most needed for investigators and study personnel jnvlufing monitors. Study participants generally appreciate PRO and are willing to comply with protocols. Providing guidance on the I,portable of completing PRO important for studies where PRO are completed outside of the study visit.
ITEM#33 Establish process for PRO assessment at (and beyond) withdrawal for patients who withdraw early from a study or who go 'off-study'/'off treatment'	• Should be patient led and standard practice that patients willing to continue completing any study outcome measure (after withdrawing from some visits) are encouraged to do so. Permission for routine mortality and morbidity data should also be sought if possible. Clearly withdrawal of patients who lose capacity is a different issue and is dealt with in the REC application. • PRO assessment will follow the same rules as the other trial procedures: in case of withdrawal every effort will be made to complete the safety follow-up procedures including PRO if they are included in the protocol procedures to be completed after study drug discontinuation • Only really applies to patients who stop study treatment, but remain in the trial, I think. Low	• is a standard section for all data items • Importance of this item may depend on Trial Duration and expected number of patients lost to follow up. I don't consider the item critical if one can reasonably expect only a small Portion of patients (let's say < 10%) withdrawing before end of study. If lots of missing data are to be expected (like in an oncology Setting) it is very important to define in advance how to cope with that. • General requirement for clinical protocols (e.g. Intention-to-treat or "per protocol assessment, management of missing data etc.). • Already captured in main SPIRIT

	likelihood of getting useful data from patients who withdraw or go 'off-study', whatever the latter means. • Not different to other outcomes. How can an outcome assessed beyond withdrawal? • But I regard this a general issue about the management of outcome data collection for such patients - nothing special for PROs. • This should also be addressed for all the data in the protocol, not just the PRO data. • It is part of the end of study, early DC schedule of events • ops manual • this is critically important in oncology • it should be part of analysis plan • If the patient with draws then the PRO assessment stops, do not believe that it is beneficial to force a patient. Patients withdrawing early did not reach the intended time point planned and the data should not be collected for the sake of collection, a final early discontinuation should focus on the patient's needs and not the study needs.	checklist • Important but very challenging and often impossible. • I don't know what this would entail. We specify time points in the protocol. Other issues regarding capturing data at these more difficult time points is handled outside of the protocol document for cooperative groups trials. • Critical in PRO as primary outcome. Important in PRO as secondary outcome • Part of 14 • if they have withdrawn, there is no further assessment unless ethics explicitly give for drop-out follow-up • Important to avoid missing data that is needed and collecting data that is not needed. Brief mention in protocol, more detail in trial conduct / staff training documents. • This missing data can provide valuable information and efforts to collect data from such patients should be carried out where possible
ITEM#34 Specify that a named person/position at each centre (and/or centrally) be nominated to take responsibility for administration, collection and checking of PROM - specify whether this is or is not the treating clinician	• As long as it is in compliance with the current legislation it will be acceptable from a regulatory perspective • No need for clinician involvement in this? • No need to include in protocol. Can be covered in separate document. • I think this is too much detail for some protocols, but would be acceptable for others. • Discussion btw Site monitor and clinical site • Important, but not for protocol • Not required in protocol - should be included in guidance notes provided to site. • depends on the instrument • This seems similar to other questions along these lines. I don't think this is feasible and in most cases the treating clinician should not be the one doing this because of social desirability bias. • Not in study protocol. it should be included in the ethical approval request • Under ideal circumstances and where the population under study is not inconvenienced yes. Practical issues would probably result in multiple persons. • A specific role may be more important than a named person. Only when required should it be the treating clinician, other site staff are typically more successful with this. This should be part of training and data management • if ePRO/VRS this may need to be someone at a data centre, following up with site staff and patients • overlaps with other questions	• I do not feel strongly that this needs to be a centre specific activity - it could equally be a centralized process. A champion at each site should have a number of monitoring points on study activity that they are paying attention to - PROs should be included in this (same as a recruitment table). • Someone needs to take ownership of this; responsibility • Would rate this as 9 if this includes checking for potential 'alerts' about patient suffering • This item need to be split in two. Specification regarding treating clinician is critical. Identification of who is responsible is more a question of monitoring procedure. • Like #30 this is very important, but it usually goes in the site training materials or start-up procedures. • Critical information to be specified in the "Methods" section • it will not be wise to make the treating clinician responsible, as this is a data management task • Management is highly variable across institutions. We don't need to tell them how to do their work. • This is completely infeasible for cooperative group trials where 100s of sites are participating and site staff is constantly changing. • This may be difficult in practice due to availability of staff and consistency in continuity of care. If there is a named person (like a cardiac liaison nurse) it may be possible. Ideally it would be great to have a named clinician/ researcher undertaking this work. • This is generally operationally generic and not protocol specific • Can be part of appendix for secondary outcome; not necessarily part of protocol. • people change • Brief mention in protocol, more detail in trial conduct / staff training documents. • Again, important but for a site manual • very important for data completion
ITEM#35 Specify how an electronic PRO system/database will be maintained and how investigator will meet regulatory requirements	• Should be covered by Standard Operating Procedures (as should many previous items). • No more or less important than any other outcome collection. Again, a lot of this needs to be in SOPs and in the Ops manual, not in the protocol • Standard procedure	• is essential particularly in ctimp trials but doesn't need to be specified in protocol • Shouldn't need to specify this as distinct from the overall responsibility to maintain study data securely and confidentially. • Applies to all projects

and ensure data integrity and security	• This is only relevant for regulatory trials which are still a small proportion of all trials. DO not confuse these two kinds of trials- the bureaucratic load for regulatory trials is too high for researcher initiated non regulatory trials, and this PRO question will result in imposition of criteria for the regulatory trials being imposed on all trials. This will reduce the number of people doing non regulatory trials. • I don't think necessary to detail this specifically for PRO if a secondary outcome measure, as data management and compliance with regulatory requirements will be covered in the description of the entire database • General data quality issue, nothing special for PROs. Details not for protocol but risk management document. • Part of TMF • Again, this should be part of the protocol in the context of ALL the data, not just the PRO data. • Important, but this is a Data Management Centre issue more than a protocol issue. To be specified in site and DMC SOPs. • Again, we treat these data like any other data collected and its codified in the CT SOPs • ops manual • Quite a few of these questions are elements already incorporated into GCP - there is no reason PROMs should be treated differently from any other trial measure	• CDISC is working on data standards in this regard as well. Marian Strazzeri at FDA can discuss more completely. • important to demonstrate how legal (and ethical) requirements will be met • Probably not needed in the protocol. • Item as worded is confusing as statement contains three components, and it is not clear if 'investigator' is clinician at centre or principal investigator responsible for entire study. • This question, also, belongs to the domain "do PRO measurements make an exception? • ...this is important in general, not specifically for PROMs, and part of GCP. • May belong to an appendix • Part of overall clinical trials unit management - not the domain of a particular protocol • This is handled outside of the protocol for cooperative group trials. • Important for all researchers to fully understand and follow due process in governance of patient data • Not protocol specific - included in separate documentation • Technical details of database set-up should not be part of the main protocol. • The appropriate maintenance and regulatory compliance for EDC systems is essential for all data captured that way. Not just PRO data. • Procedural issue better suited to document other than protocol.
ITEM#36 Specify plan to monitor PRO compliance, including adherence to time windows	• Could be detailed in monitoring plan rather than protocol. • 'Monitor' has a very specific meaning in clinical trials. I do not think it is sensible to require source document verification of completion of PRO. Again, this probably belongs in the trial SOP and central study manual, rather than in the protocol. • No need to include in protocol. Can be covered in separate document. • This depends on whether the trial is more pragmatic or more explanatory. If the former, little monitoring, if the latter, lots. • General data quality issue, nothing special for PROs. Details not for protocol. • TMF • This info is traditionally in the Study Monitoring Plan, not the protocol. • Important, but no more important than adherence to data collection of other protocol objective. Need not be documented in protocol. • Not in protocol - would include in trial operating procedures • too much for a protocol - op manual or data management plan instead • Is a monitoring plan part of a study protocol? • Important - especially if several PRO are used (paper & pencil version) • Non-compliance should be viewed more in terms of over planning or a measure of a trial PRO not taking into account practical study population aspects. Monitoring is different in that it is critical and protocol (study planning) adoption should be flagged if PRO compliance is experienced in more than 10% of participating patients. • Data Management Plan • Seems to be a bit of overlap with other items	• This seems duplicative of an earlier item about time windows. Perhaps combine the two together? • should be covered in statistical monitoring plan • This may depend on the degree to which this matters for the analysis of the particular PRO. • If other items are in the protocol (see above) failure to adhere breaks protocol so shouldn't happen. Would hope that plans in place to monitor adherence to protocol throughout and not just in relation to PROs • Existence of plan should be mentioned in protocol, but plan should be detailed elsewhere (monitoring guide, etc.) • Very Important. Also becoming important is a possible system of real-time reporting of severe PRO symptomatic adverse events that could trigger interaction with the healthcare team to evaluate for possible supportive care • Like #30 this is very important, but it usually goes in the site training materials. • I interpret the Item within the context of a central office responsibility, rather than something personnel at participating centres are expected to do • Typical CRO activity: However, such monitoring can be implicit in small size/one Centre studies or, when the schedule is forced (e.g. measurement ad admission/discharge) • This is handled outside of the protocol for cooperative group trials. • Helpful to outline this process in both primary and secondary outcomes. • Important issue, but is really quality assurance. Brief mention in protocol, more detail in trial conduct / staff training documents. • Again, important but for a site manual

ITEM#37 Include an overview of PRO administration (data collection), and data handling/transmission and storage procedures	• Should be covered by Standard Operating Procedures (or within previous items). • No different to standard process • Wasn't this covered already in a previous item??? • not specific for PRO • General data management issue, nothing special for PROs. Details not for protocol. • TMF • Important, but goes in site and Data Management Centre SOPs, not protocol. • data management/ops manual • part of ethical procedures • Important for protocol to inform external research governance reviews.	• If done thoroughly, this item will require what is asked of some of the other items. Try not to be redundant in the final version of the checklist. • Not sure this is PRO specific, wouldn't it be covered more generally? • how does this differ from item #35 • duplicates previous (or so it seems to me) - SOP • Monitoring guide. • Mandatory for multicentric trials; optional if not implicit in small/one Centre trials • Too detailed in my view. • This is generally a standard part of IRB applications. I'm not sure if it is generally part of the protocol document or not. I am assuming not with my answer of 1- but if this is part of every protocol, then it should be true for protocols that include PRO data no less than for others and I change to a 9. • This is handled outside of the protocol for cooperative group trials. • I think this info is critical for primary outcome and helpful for secondary outcome. • This can be part of an extra summary document but not necessarily part of the formal protocol. • Brief mention in protocol, more detail in trial conduct / staff training documents. • Again, important but for a site manual
ITEM#38 Ensure plans for administration of PROM(s) are consistent with each PROM's user manual	• or document any variations • Specification and consistency across sites more important than adherence to user manual. • Too detailed. • Don't see how a protocol can "ensure" anything - this sounds like the role of someone appraising a protocol. • IM • This may be unintentionally strict - if the administration differs, the investigators need to explain why / provide the rationale. • This should be done centrally by the CI and any tensions/clashes resolved. A clear plan for administration within the context of the specific study should go to the sites. • Not a protocol issue - more of an implementation issue. • Not in protocol - should be done when selecting PROM • First, user's manuals will not always be of good quality. so issue is not consistency, but administration of proms should be explained • Or, if not consistent with something in the user manual, provide a rationale for why not. • All details related to administration of PROM(s) should be in one place only, ideally the user manual. These details should be omitted from the PRO protocol. • In the protocol, this item should be more explicit, e.g. how this will be ensured. • Where user manuals exist - don't think the necessarily do for all PROMs • Important for protocol implementation but not sure this needs to be in the protocol	• This should be done but not sure it has to be specified in the protocol. • I think this depends on the context of the use - • More of GCP (Good Clinical Practice) • This seems very wise. It should be for the researcher to do, not the REB or other reviewers. • Or if not consistent, also discuss why not. The User Manual should be in an SOP or appendix to the protocol. • should have SOP for this • This item should be related to item 23-29? • Or if not, a rationale for why it deviates from the user manual • This is the protocol developers' responsibility. But I don't' think it belongs in the protocol itself. Very important!! • Implicit in item #37, therefore redundant • Micromanagement • While this is a good idea scientifically, I don't think that this should be part of the checklist. Many PROMs don't have user manuals. Also, this doesn't require text in a protocol (so nothing to check off). • Important that info is aligned with guidelines in both primary and secondary. • assuming the user manual includes this information • This needs to be checked but not necessarily stated in the protocol. • Brief mention in protocol, more detail in trial conduct / staff training documents. • Again, important but for a site manual • and that permissions to use these PROMs have been given • It is conceivable that a study may collect a PRO in a manner not consistent with the PRO user manual. The checklist item should focus on cases when this is required and encourage protocols to state rationale for deviation from user manual.
ITEM#39 Include an a	• if secondary this is often mainly in the SAP	• This could be described in the SAP.

priori description of all planned PRO analyses pertaining to the study hypotheses	n.b. where more detail of primary PRO analysis is also expanded on • Standard procedure • Why should these be described any differently from trials with no PRO? • Details for the SAP, not the protocol. • While a high-level description should be in the protocol, the details are usually provided in the Statistical Analysis Plan. • Clearly essential to have a plan and avoid 'data dredging' but should not be so inflexible that an emerging and valid new question is not explored - after all research is about exploring and learning. • Essential for evaluation of overall results • The stats plan is separate from the protocol though generally a high level overview is provided in the protocol itself • Statistical Analysis Plan document. Could be in the protocol, typically in SAP only • Could be part of statistical analysis plan. • The word "all" is too restrictive. Include an a priori description of the primary PRO analyses.....	• The protocol should signpost the location of PRO analysis details i.e. in the SAP • will be fully covered in a statistical analysis plan which has to be written within 3 months of study start • don't feel qualified to comment on this so please discard my answer • Critical • Why a " a priori"? PRO ae "method" and should be placed in the Methods section like any other measurement procedure. • Already captured in main SPIRIT checklist • For primary outcome, the primary analysis needs to be defined in the protocol. All else should be described in a statistical analysis plan, not in the protocol. • At a high level. More detailed descriptions would be expected in the statistical analysis plan post-completion • Yes, but let the possibility to complete the PRO statistical plan during the study (before the "freeze" of the database and before revealing the double-blind). Some a posteriori analyses (e.g. other definitions of responders to make sensitivity analyses) may be also accepted if clearly disclosed as ad-hoc non pre specified analyses • The detail should be included in the statistical analysis plan (SAP) - determining this detail (esp. "all" planned analyses) may hold up protocol completion. An overview of key aspects of the plan are required in the in protocol is needed when PRO is primary. Aside: revised wording to this effect may change panels' voting. • Is this the same as a Statistical Analysis Plan (SAP)?
ITEM#40 State the assumptions of PRO analyses	• in SAP for secondary • Briefly in protocol, should be covered in Statistical and Health Economic analysis plans. • A bit vague for implementation. Needs clarification of what is meant by 'assumptions'. • Too detailed. • Details for the SAP, not the protocol. • These details are usually provided in the Statistical Analysis Plan. • I'm not sure what this means exactly - too vague • With references if possible • this is an SAP issue • Unclear question. What kind of assumptions? • I don't understand this. Do you mean hypotheses? • Not sure I understand the intent of this statement	• Could be described in the SAP. • It will be interesting to have a statisticians views • probably better covered in statistical analysis plan • Must be made clear • ditto Q39 • #40 could be combined with #39 when expressing best practice. • This item is not really clear to me. I assume that "statistical" assumptions are meant, here. • Redundant. Issue already dealt with in previous items • Vague • At some point, we have to trust that RCT biostatisticians are competent and understand how to do statistics. If not, that is a different document to be developed and not part of a protocol checklist. • These are often obvious (e.g., standard assumptions for statistical testing). • including the nature of the data • This detail is for the SAP. • Not sure what is meant here. • I am not sure what this means
ITEM#41 State the anticipated response rate and implications for the sample size	• Anticipated response rate doesn't seem relevant but a statement that addresses the plan for addressing attrition e.g. replace subject or intention to treat approach; incomplete cases AND how the data will be handled.	• Could be included in the SAP. • It will be interesting to have a statisticians views • If exploratory as a secondary outcome, may not be critical. • Allow for over optimism! • This should already be integrated in sample size calculations, as specified in item 17. • Though important at analysis to think

		about this I'm not sure how useful in the protocol as it will just be conjecture at that stage and could be vastly different • General requirement for clinical research protocols • Already captured in main SPIRIT checklist • I think it's important to justify your sample size. How you do that (i.e., whether you adjust for missing data or not) should be up to the protocol authors. The checklist shouldn't specify how to do this. • This would go in the statistical analysis plan. It could also go in the protocol for a primary endpoint. • if a PRO is not the primary endpoint sample size calculation ned to be discussed in relation the primary endpoint as well,
ITEM#42 Include an a priori estimation of PRO effect size	• This need to be clearer: do you mean estimation by a comparison of treatment groups, or do you mean a guess based on prior (indirect) information? • Not needed for secondary if no power calculation is being made for secondary. • Essential for primary. See previous comment about describing power for secondary outcomes. • Again need to have this but centrally. Sites need to be encouraged to achieve maximal completion. • Clinical meaningfulness should be a given if a validated PRO is used and should be easy. If it is being used as a primary outcome for the first time then the effect size must be estimated as it is part of the hypothesis to be tested. • Only needed it the PRO is being used to calculate sample size as a primary outcome; maybe a key secondary outcome.	• It will be interesting to have a statisticians views • Goes hand in hand with sample size calculation; however irrelevant to trials wishing to simply canvass the trajectory of key PROs • Again, think this is already embedded in power/sample size calculations. • Effect size won't be applicable for every analysis, e.g. delaying time to deterioration may be the aim • Prefer to see mean and SD or other distributional information separately, not rolled together in a single effect size. • ditto Q39 • More important is the a priori support for a meaningful change for the measure (see #49) • Not critical, if significance rather than ES is aimed at. • ES must be discussed but not represent an a priori estimation. • Already captured in main SPIRIT checklist • For this item too, I think it's important to justify your sample size. How you do that is up to the protocol authors. • This seems redundant with a sample size calculation item • Is part 3-4-5? • one can hazard a guess but it won't be an estimate • or a plan for how to assess this if this information is not available
ITEM#43 Specify intention-to-treat or per-protocol PRO analyses	• Briefly in protocol, should be covered in Statistical and Health Economic analysis plans. • This should be for the efficacy analyses in general, not separately for each PRO analysis separately. • Why should this be any different for PRO trials? Of course this is needed, but it makes me think that I am not understanding the point of this survey- I imagine anything in the existing spirit is remaining the same, and this spirit PRO is for extra requirements? • Details for the SAP, not the protocol. • Good clinical practise	• It will be interesting to have a statisticians views • presume the same should be done for PROs as for other endpoints; may not be necessary to state as checklist item • similar to item 49 • Generally it is neither ITT or Per Protocol- it is the population with at least a baseline and post-baseline assessment when analysing over time unless using imputation. I would reword this to state the analysis population for the PROs • this needs to be tied to timing issue • General requirement for clinical trials. This item seems redundant (see prior items) • Already captured in main SPIRIT checklist • ITT is an ambiguous term -- better to say 'as-randomized or per-protocol' • This should be defined in a statistical analysis plan, not in a checklist. • Depends in study. If possible, yes. Not always possible. • Or both, depending on specific

		circumstances. One of these should be used for PRO as primary outcome • Rephrase as more general "include definition of the analysis population" • For SAP. • For most efficacy analyses, it is the ITT that is preferred.
ITEM#44 Include a priori identified summary statistics (as appropriate)	• These should all be in the SAP. In reality SAP is usually written after the protocol and before looking at the data. • Details for the SAP, not the protocol. • This is an SAP deliverable, not a protocol issue • Summary of what? • this is more suitable for the SAP than protocol • Unclear question. Do you mean that you should specify whether you will going to report means or medians? • Do not fully understand this item - left blank intentionally • Important to identify which of the PROM scores (total or subscale) will be used in the analysis.	• This could be detailed in the SAP. • It will be interesting to have a statisticians views • This would be addressed within the analysis plan; i.e. some overlap with item 39 • I don't grasp what this item involves. • defer to methods here • Not clear what is meant. Is this to enable an adequate sample size calculation? • redundant with item #39 • Again not entirely clear what you mean, outline the analysis plan including descriptive? • item not clear • ditto Q39 • "As appropriate": how can we respond to question, then? This should be part of the SAP. • I can't tell what this means • General requirement for clinical trials. • Vague • The "(as appropriate)" makes this item non-understandable for me. • Combine with checklist item #39? If a summary measure is used, it should be clearly specified in the analyses. • If part of the primary analysis, then yes. • For SAP. When PRO primary, may be useful to specify in protocol as it flags how the PRO data will be used - e.g. trajectory of means over time versus time to deterioration in PRO are very different uses of PRO data. • This is for the statistical analysis plan. • will be implicit for primary in the same size calculation • Not sure what's included here?
ITEM#45 Specify the minimum PRO response rate and acceptable degree of timing deviation (i.e. acceptable time windows for each PRO assessment timepoint) before the PRO objective is compromised	• Dealt with above. • Acceptable windows for data collection and item response rates for inclusion yes, but not a hard cut-point for 'PRO objective is compromised'. • No need to include in protocol. Can be covered in separate document e.g. Statistical Analysis Plan at least for a secondary outcome. • SAP not protocol • Again more for SAP • Should be the same as with non-PROMs.	• It will be interesting to have a statisticians views • overlaps with item 14 • better covered in stats analysis plan • The team that controls this should not have to initiate this if the job is done in a planned , controlled and efficient way • Timing is redundant with #14. • I don't think this is needed up front, at no point do we really want to shelve the data, we just need to adapt the analyses appropriately and adequately look into the possible biases and highlight limitations • important but should be included as part of answers to previous questions • Should be mandatory in the SAP. Not in protocol. • 'Before the PRO objective is compromised' would benefit from clearer specification • General requirement for clinical trials. • I would split this item. The "Minimum response rate" should not be defined a priori. The number and type of responders represent information in themselves. How much the response rate biases the results is another issue • timing deviation- important but sensitivity analyses can be performed so not critical • If you have this great, but this kind of information is very difficult to come by, especially when you are dealing with new

		treatments or new patient populations. • I would never lock myself in with a hard cut-off on response rate. Also, I only specify windows for studies involving FDA label claims. Otherwise, I think some flexibility on the backend is optimal. • not sure how you would do this in many circumstances • This seems more an issue for a data monitoring committee guideline than for the protocol. • I find this item confusing. Double-barrelled too. • Might be more relevant for SAP or site manual • Do you mean per item or overall in the study population?
ITEM#46 Describe methods for scoring endpoints. Where possible, reference scoring manuals for summated scales from PROM (domain-specific and/or total) and methods for handling missing items, and methodological papers for composite endpoints (e.g. QTWiST)	• Briefly in protocol, should be covered in Statistical and Health Economic analysis plans. • Not in the protocol • Cite references describing methods, no need to include details. • This information would probably be more appropriate in a DAP. • While a high-level description should be in the protocol, the details are usually provided in the Statistical Analysis Plan. • if not there results may be meaningless • typically the PRO and the scoring manual are protocol appendices • This information could be in an appendix or via hyperlink • Could both be in a separate document	• Could be detailed in the SAP. • It will be interesting to have a statisticians views • better covered in detail in analysis plan • I don't fully grasp what this item involves. • For statistical analysis plan -not protocol • should go in the SAP • SOPs • Should be mandatory in the SAP. Not in protocol. • Or the SAP??? • Just a reminder is necessary, if PRO are validated in the literature (so that manuals exist). • Could be included as reference. • Brief mention in protocol, more detail in SAP. • not sure what is meant by an endpoint in this context
ITEM#47 State statistical significance levels and include plans for multiplicity/controlling type 1 error.	• A lot of this is needed for SAP - perhaps not a protocol checklist. In an ideal world you may like but your trial set up times will be really long. • Briefly in protocol, should be covered in Statistical and Health Economic analysis plans. • As in all trial protocols....?. • For primary, should be described for sample size justification (significance level, no multiplicity). For secondary outcomes, details are for the SAP, not the protocol. • This element should be included in the protocol for ALL the data, not just the PROMs. • High level in the protocol, detail in the SAP • Confidence interval more important than p-value • Might be #48 • Both error types (I and II) should be controlled by a presented a priori sample size calculation. First type 1 error has to be estimated according to amount of hypothesis/tests, than a sample size calculation considering type 2 error should follow including type 1 error estimate.	• Could be detailed in the SAP. • It will be interesting to have a statisticians views • for secondary analysis might be better in analysis plan • I don't understand this item. Perhaps it would be fine to include either 47 or 48, or include a more general item about any plans to address the multiplicity of PRO data? • This is linked to a lot of the statements as statistical sampling is one of the cores of the project • not a PRO question but CGP • ditto Q39 • Again, nothing new in clinical trials. • At some point, we have to trust that RCT biostatisticians are competent and understand how to do statistics. If not, that is a different document to be developed and not part of a protocol checklist. • For secondary endpoint, depends on type of objective. • Brief mention in protocol, more detail in SAP. • One of many questions that overlap with SPIRIT. is the intention that this guideline will complement SPIRIT or replace it for trials with PROs. I'd assume the former. • This need to be related to the overall study as well. • IN the regulatory context, this must be done for FDA. However, personally, I do not think it should be required for secondary endpoints. • For secondary endpoints, these should be stated in either protocol or pre-specified SAP
ITEM#48 Pre-specify sequence of	• Should be covered in Statistical and Health Economic analysis plans.	• Could be detailed in the SAP. • It will be interesting to have a statisticians

testing/exploratory analyses to control for multiplicity or pre-specify domains (e.g. in a regulatory trial/labelling claim)	• Difficult to see how a primary outcome could be exploratory? Details for the SAP, not the protocol. • This element should be included in the protocol for ALL the data, not just the PROMs. • SAP though hierarchy of endpoints is listed in the protocol • This should be in the detailed analysis plan, not necessarily the protocol. • Not really sure what this means - when does one assume "testing/exploratory analyses" in a clinical trial? • depending on whether a claim is pursued or not	views • I think the wording of this item requires clarification; although having said that I think this item is redundant if item 47 is included • Question unclear • This is just one way to address item #47. • not a PRO question but CGP • ditto q39 • My preferred answer would be: "it depends on the type of trial and research question". • These seem like 2 different questions. But to me "exploratory" means "exploratory" and not "pre-specification." • If using an alternative strategy for handling multiplicity, then this checklist item is irrelevant. Consider deleting, because it is redundant with #47. • Could be part of SAP instead of protocol • Aside: not sure how this applies when PRO is primary. • This need to be related to the overall study as well. My experience is that PROMs (compared to other endpoints) sometimes were excluded since it was stated there would have been problems with mutiplicity otherwise.
ITEM#49 Specify the criteria for clinical significance (e.g. state minimal [clinical] important difference and/or responder definition (size and duration of benefit)	• Usually more hypothesis generating as a secondary so not relevant in so situations and/or include outside of protocol - i.e. in SAP • Briefly in protocol, should be covered in Statistical and Health Economic analysis plans. • This is patient reported after all • When available. • Should be in the sample size justification for a primary outcome PRO. Not particularly relevant for a secondary outcome. • Depending on the PROM and the specific research question, it may be difficult to do this. • This is important but not always available particularly for newer measures, if not available should not mean the measure cannot be used • we power primaries for the MCIDs • Not always possible • MCID and responder definition more likely to be available for size of benefit, less common for duration of benefit (although that would seem important too) so may be hard to make that second element critical. • This should always be pre-specified. • When relevant to the hypothesis - otherwise, not required.	• To me this is more important that statistical significance from an applicability of findings standpoint. • It will be interesting to have a statisticians views • ditto Q39 • To be mentioned in the protocoled, and detailed in the SAP. • Exception: if trial is contributing to evidence base on MCID. • A very neglected issue. My score should be "10" if available! • Already captured in main SPIRIT checklist • One of the most important parts of the protocol. • Very important • only if calculated on the metric • When PRO is secondary, still required, but brief mention in protocol, more detail in SAP. Critical when PRO is primary - to defining the endpoint and sample size. • not sure why this is wanted beyond info in sample size calculation • very important and to link these to potential claims • Either SAP or protocol for secondary endpoints
ITEM#50 State how missing data will be described	• Again - you don't seem to be linking protocol and its checklist with the SAP • Briefly in protocol, should be covered in Statistical and Health Economic analysis plans. • Details for the SAP, not the protocol. • I would expect this in the analysis plan not necessarily in the protocol itself.	• Could be detailed in the SAP. • This also ties closely with item #46 - for example when a score cannot be calculated when not all items are responded to based on criteria. • It will be interesting to have a statisticians views • Item wording needs clarification. Wondering whether the protocol checklist should specify that reasons for missing data should be collected, and description of missing data applies to the publication or trial report? • cover in analysis plan • If include item 51, then this item could be left off. • Specified in statistical Analysis plan • ditto Q39 • To be outlined in the protocol, and detailed in the SAP • Nothing new • There is already (earlier somewhere)

		discussion of missing data. Don't understand what you are calling for here is a "description." A lot of times, you don't know ahead of time how much missing data there will be, whether they are informative or random, etc. until the data are collected. Not sure how a checklist item is helpful. • Could be part of SAP instead of protocol • Belongs in SAP. • This is for the statistical analysis plan. • Important but maybe for the SAP • Not specific to PRO. Unsure what is expected here beyond frequency. • Either SAP or protocol
ITEM#51 Describe method for handling missing assessments (e.g. approach to imputation and sensitivity analyses)	• Briefly in protocol, should be covered in Statistical and Health Economic analysis plans. • Details for the SAP, not the protocol. • SAP • This information would probably be more appropriate in a DAP. • While a high-level description should be in the protocol, the details are usually provided in the Statistical Analysis Plan. • SAP • Important but should be brief in the protocol and more detailed in the SAP. • Could be stated in statistical analysis plan. • As for item 50	• Could be detailed in the SAP. • It will be interesting to have a statisticians views • cover n analysis plan • Specified in statistical Analysis plan • Also need to describe how to handle missing items. • ditto Q39 • Nothing new. This items seems redundant (See prior "statistical" items). In other words, some of these items seem to test the general competence of the authors in trial design, not their specific competence in PROs. • Already captured in main SPIRIT checklist • But this should be in an analysis plan. • A lot of times, you don't know ahead of time how much missing data there will be and how you're going to handle them. Unrealistic to ask someone to specific this a priori. • Could be part of SAP instead of protocol • Brief mention in protocol, more detail in SAP. • This is for the statistical analysis plan. • Important but maybe for the SAP • Either SAP or protocol for secondary endpoints
ITEM#52Describe the role of the Data Monitoring Committee and Quality Assurance for PROs	• Should be covered by overall trial consent process, patient information sheet should include details of PRO assessment • Part of participant information, not an item for the protocol itself. • Do not understand the question. There is informed consent for the trial which covers all outcomes. Nothing specific for PROs. • Don't understand why this is a special issue for PROs. • The informed consent process is not specific for PRO assessment • The ICD is a separate document and managed under a separate SOP from the protocol • too much for a protocol in detail but make sure it is covered in the consent document and ops manual • Not sure - would generally assume that one overall consent form would include a description of the PRO assessment part of the study. • If the PRO is not linked to a specific therapy decision it is important. If linked to therapy decisions primarily then it is critical. • This should not be separate from the study informed consent • Should be within the overall informed consent as a section. • Not specifically different/separate to informed consent for use of other clinical data. Should just be covered in standard trial info and consent for what participation involves. • Should this be "describe the procedure for PRO assessment in the informed consent form/process?	• Could be included in the DMC Charter/plan. • not for protocol but can be in terms of reference for dmec. • Unless there is some specific role related to PROs, I don't think specific DSMB language related to PROs is needed. • Should be in monitoring documents. • Nothing new. However, the DMC role is well defined in the literature. • If a PRO is a primary outcome, it should be treated as any other primary outcome, with the DSMB invoking stopping rules, etc., as appropriate. For PRO secondary outcomes, part of the evaluation for the primary (non-PRO) outcome may involve reviewing the secondary outcomes, and my understanding is that DSMB could call for further analysis, termination of assessing that endpoint b/o poor data quality, etc. In short, PRO endpoints should be handled by DSMBs the same way as are other endpoints. • This is handled outside of the protocol for cooperative group trials. • Overlaps with 45, 23, 30 and 31. • Warrants mention in protocol, and more detail in other trial documents, as appropriate. • Important but for site manual or monitoring plan • sounds like 2 separate questions. unsure why DMC has any specific role re PROs beyond general responsibilities

		• Is there always such a Committee?
ITEM#53 Include an a priori plan for consistent/standardised management of PRO alerts (symptoms reported by patients that exceed a pre-defined level of severity) to be clearly communicated to all appropriate trial staff	• Where appropriate - not required for all PRO assessments • Ops manual, not protocol	• only if this is applicable • Cannot assume that clinical trial PRO data will be available clinically. • If applicable for that instrument? • Clearly critical but does the field currently have a sound approach towards this? • Should be in monitoring documents. • If this a PV question, it should be explicit. • Depends on the trial. I think it's preferable for there to be other clinical systems in place that don't depend on the study conduct. • Nothing new • ...this relates to SAE reporting when PROs are secondary outcomes. • This should include a statement even if no alerts are to be done. • With rare exceptions (e.g., some depression scores that indicate the patient is at risk of harm to self or others, which have been used in psychiatry as alerts for many years), I don't believe the field is at a point where we have reliable and valid PRO data and cut points that can be used for alerts on an individual patient basis. At the present time, doing this would go well beyond the data. • Very important that PRO tools are also clinically useful in real time to help patients who have difficult symptoms • This seems like a very specific requirement which is not applicable to most protocols. Also, this can be very specific to local IRBs. • Not certain is this is for protocol or for training documents • Dependent on trial setting. • Brief mention in protocol, more detail in staff training documentation. • Important but for site manual or monitoring plan • Make sure to - if possible - relate to previous studies and literature when setting these cut offs. Can these be established for an instrument and population like MIDs or should it be done on a case by case basis in the specific study? • Trial staff need guidance on this matter, and management should be standardised
ITEM#54 Describe informed consent procedure for PRO assessment.	• Should be covered by overall trial consent process, patient information sheet should include details of PRO assessment • Part of participant information, not an item for the protocol itself. • Do not understand the question. There is informed consent for the trial which covers all outcomes. Nothing specific for PROs. • Don't understand why this is a special issue for PROs. • The informed consent process is not specific for PRO assessment • The ICD is a separate document and managed under a separate SOP from the protocol • too much for a protocol in detail but make sure it is covered in the consent document and ops manual • Not sure - would generally assume that one overall consent form would include a description of the PRO assessment part of the study. • If the PRO is not linked to a specific therapy decision it is important. If linked to therapy decisions primarily then it is critical. • This should not be separate from the study informed consent • Should be within the overall informed consent as a section.	• Should be included in the PIS as a protocol appendix. • This is an Ethical point and it would be interesting to hear the HRA's views. • only if differs from main consent procedure • Included in consent document • This is not specific for PRO assessment • Should just be integrated with all the other issues covered in the consent. PROs should require specific, separate consent. • To me this is part of the overall consent procedure and not necessary to pull out separately • Informed consent for the general study suffices. • should be included as part of general description of consent - I do not think that this should be over burdensome, however, Need to think carefully about how much information is included in PIS • Should be incorporated in standard trial information, not as an 'add on'. • Nothing new • Already captured in main SPIRIT

	• Not specifically different/separate to informed consent for use of other clinical data. Should just be covered in standard trial info and consent for what participation involves. • Should this be "describe the procedure for PRO assessment in the informed consent form/process?	checklist • Not sure that a specific PRO consent is always needed - this seems to be implied by the question. • This is a standard part of clinical trials. • They have consented to be in the trial - that includes consent to complete PROs. Completion of PRO is itself an act of consent. • This is a local IRB issue and not standardized at the protocol level. • Is this procedure or content of the informed consent? • For secondary endpoints, the informed consent procedure will cover all data collection, not just be specific to the PRO data. • Important but belongs elsewhere. Perhaps just note that PRO assessment should be included in consent procedure in protocol? • Why would you need informed consent for PRO assessment? • Wouldn't this be include in the overall ICF for the study? • Do you seek consent for each PRO or for participation in trial? • Isn't it usually included in the overall consent or assent for the study? The Assent procedure needs to be described as well. • Assent is the agreement of someone not able to give legal consent to participate in the activity. Work with children or adults not capable of giving consent requires the consent of the parent or legal guardian and the assent of the subject.
ITEM#55 Specify whether PRO forms will be used to influence therapy or patient management (i.e. will the clinician use PRO responses to inform the patient's care?). State the assumptions of PRO analyses	• although unusual • If yes, then the PROM is part of the intervention, not (just) an outcome measure, and needs to be carefully specified. • What is the difference to other outcomes here? • But issues the same as when any other "investigation" influences treatment? • Not usually possible or done in oncology trials • This relates to the question re: if the site has access to and reviews the PRO results. Generally, we make an effort to avoid this whenever possible. • If this occurs, it would be mentioned in protocol. However my rating is not meant to say that this should be done. If an efficacy clinical trial, there is not supposed to be sharing of data with the clinician as it could lead to unblinding. I think this is a risky thing to include. • Important if applicable - generally presumed to be not applicable in most trials if there are standard elements of blinding involved. • no, measurement error is likely to be too high • If a PRO has a primary objective yes. If the PRO is being used as a secondary outcome and for a secondary objective only if it should not influence therapy or patient management as a main driver. • if PRO is primary outcome, it should not influence the management/care • Bit tricky this one, not sure how to rate. Use of PRO forms to inform patients care may compromise their validity as trial endpoints. Will the patient answer differently if they think PRO info is going to their treating clinician e.g. play down symptoms so as not to be taken off trial treatment, mis-report adherence • This would be essential for inclusion in the protocol if this was the case.	• Part of the study design (noted in a prior comment as well) • Insufficient guidance/guidelines to support this activity and dialogue with physician • I assumed you are referring to post-study patient care • redundant with #53 • relates to previous question on alerts • When this is the case, the adaptive design must be detailed and explicit, and impact on evidence generation need to be discussed. • I understand the question is if the influence on therapy or Patient Management is that during the study (and not afterwards after having analysed the results) • It depends on the aim of the PRO measure. Implicitly, if therapeutic use is not specified, you need not to write it! • Any data measurement could influence care in a trial (e.g. harms) • If this were to happen, it has to be communicated as part of informed consent. This should not be a separate "item" - it is covered by the standard consent procedures. • Not sure how to answer this, so didn't. This is particularly going to be an issue when PRO-CTCAE is used, compared to other instruments used for database purposes. • Depends upon nature of study • Not common to use PRO responses to inform a patient's care. If that is the case, then certainly it should be mentioned in the protocol. But if not the case - not needed in protocol, but important in patient information sheet. • Do you mean during the study or when implementing the results?

		• As this can introduce treatment variation and bias findings, it is important to note for any assessment whether the study personnel are allowed to review, expected to review, and altering treatment based on PRO.
ITEM#56 Include detailed plans for regular feedback to participants via letter/newsletter on PRO aspect of study.	• Should be included in overall study communication strategy • Good practice, but not for inclusion in the protocol. • Regular feedback about PRO during the course of the trial is unnecessary and inappropriate for most trials. Feedback on the trial is appropriate, but not the PRO specifically. • ??? What is the difference to other outcomes here? • This is not specific to pros, should apply equally to all trials. • I don't agree with "regular feedback" during the study - unless this is simply about levels of completion / quality as a method of encouragement to adhere. • Not part of a protocol, • Ideally treat the PRO as an integral and equally important part of the overall results within a newsletter reporting on the study as a whole. We need to see PROs as part of the whole - avoid separating out this aspect. • Should be for whole study • often this is a process implemented to motivate compliance with PRO completion, particularly in the context of APP based daily diaries • This could cause unblinding in an efficacy trial, so it should be done with caution and only at the end of the study. • I do think this is a great idea and perhaps would make patients more likely to complete PROs on a regular basis if they are given feedback at intervals • Critical at the end of trial. Critical not to give feedback during a running trial to avoid influencing individual patient behaviour • Participants as in site staff responsible for PRO completion or patients? Wasn't sure how to answer, value in regular feedback on PRO completion rates and data quality to site staff responsible for PRO completion but unsure of value/appropriateness otherwise. • Not necessarily in the protocol but good to have considered rather than leaving to arbitrary decision	• I think this is good research practice in general. I think more importantly is addressing how participants will interface with their personal data and governance as part of the study. • Not important in terms of approving a clinical trial. • Important to indicate whether regular feedback is justified, and if it is to describe the plan for that. • Question unclear: Is this for the study centres or actual study subject? If latter, not important. If former, important. Also not an essential component of protocol document but is an essential tool for study conduct. • There may not be feedback, also. Must consider trial blinding. • I wonder if we may introduce Hawthorne effect. • Participants should get results but not clear that 'regular' is achievable - surely this depends on how analysis is being done? • Critical in the era of patient-centred care. But details don't need to be in the protocol, rather in the monitoring documents. • Could help compliance • Feedback on the trial is reasonable, but I don't think it makes sense to focus separately on PRO specific-feedback, even if PRO is the primary outcome. • Totally optional. • Of benefit, but does not need to be included in protocol • It depends, again. If the patient must remain blind, feedback should not be provided. I think this item is redundant • Too prescriptive • I favour this - but it's not part of the protocol. • Will help completion of PROs at future time points if patients can see that their data is being used. • While this is a great thing to do, it cannot be detailed in the protocol prospectively. Any communication to patients need local IRB approval of actual text, which would not be available at time of study activation, nor would it be efficient to amend the protocol each time. Much easier to release a protocol communication. • not generally specified by protocol • A summary at the conclusion is desirable versus "regular feedback to participants" • Trial-dependent but need not be part of protocol. • Problematic ethically and logistically. Trial co-ordinators of multi-site trials often do not have access to patient contact info (to protect patient privacy). • Do you mean during the study or after study end? • Important for informed consent regarding promise to patients and if part of intervention to ensure study personnel recognise and adhere to protocol requirements to provide feedback to patients, Whether detailed description is required depends on the role of feedback in the intervention.