BRIEF REPORT

ASPECT-R—A Tool to Rate the Pragmatic and Explanatory Characteristics of a Clinical Trial Design

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ABSTRACT

Objective: Clinical and observational trials can be broadly categorized into having explanatory or pragmatic approaches with specific trial designs located somewhere along this spectrum. Two 10-domain instruments, the PRECIS and Pragmascope, have been developed to facilitate clinical trial design within a framework that is either more explanatory or pragmatic.

Design: We have adapted the PRECIS and Pragmascope instruments to permit both design support and *post-hoc* evaluation of clinical trials and to improve consistency of use and interpretation across raters. This adapted instrument, A Study Pragmatic-Explanatory Characterization Tool-Rating—or ASPECT-R—is described.

Results: Adaption of the PRECIS and Pragmascope instruments included reducing the 10 original domains to six. Each of the six ASPECT-R domains has a definition of domain terminology and detailed descriptive anchors. The domains are rated from 0 to 6, where 0 is considered extremely explanatory and 6 extremely pragmatic. Using an Excel®-based file with cover page cells for entry of the study objective(s) and study population of interest, the ASPECT-R instrument has individual domain-related worksheets where the user rates each of the six domains. Each of the six domain worksheets has a section provided for the user to summarize and record the rationale for their domain scoring. Each domain worksheet page also contains a radar graph that auto-populates each of the domain ratings as the user completes these ratings.

Conclusion: This new tool, ASPECT-R, should provide a reliable, objective way to rate studies along the explanatory-pragmatic spectrum that will better support trial design and facilitate interpretation of completed trials.

The complete ASPECT-R tool and guide materials can be accessed online by clicking or visiting this link: http://innovationscns.com/aspect-r-tool-and-training-materials/.

INTRODUCTION

Clinical trial designs differ considerably with respect to

whether they are conducted under highly controlled and defined conditions (explanatory) or more broadly reflect real world circumstances (pragmatic). These different approaches to trial design are generally aimed at addressing different questions with varying strengths and limitations and differences in extent of generalizability. These differences in trial design may substantially impact results even when similar interventions or treatments are compared. Failure to consider the differences in trial design may lead to misinterpretation of individual studies and when studies are analyzed as a group (as in meta-analyses). Because specific trials are designed on a spectrum of "explanatoriness" or "pragmaticness," methodologists have begun to develop instruments that facilitate identification of key explanatory and pragmatic elements in clinical trial designs.[1,2] By standardizing the characterization of study designs, they can support researchers, clinicians, healthcare providers, and policymakers in understanding and interpreting clinical trial results, particularly with respect to their generalizability to real world clinical practice.

The PRECIS (Pragmatic-Explanatory Continuum Indicator Summary) tool has been described by Thorpe et al as an instrument developed to assist researchers when designing trials along the explanatory-pragmatic spectrum.[1] This tool captures information along 10 study design domains: Practitioner Expertise (experimental); Flexibility of the Experimental Intervention; Eligibility Criteria; Primary Analysis; Practitioner Adherence; Participant Compliance; Outcomes; Follow-up Intensity; Practitioner Expertise (comparison); and Flexibility of the Comparison Intervention.[1] The PRECIS tool has been adapted as the Pragmascope by Tosh et al with the addition of a 6-point (0 to 5, very explanatory to very pragmatic) visual analog rating for each domain.[2]

TABLE 1. ASPECT-R domains and definitions of domain terminology*

DOMAIN	DEFINITION OF DOMAIN TERMINOLOGY
Participant eligibility criteria	Considerations include the intended treatment population of interest that has been identified by the study's authors (e.g., in the study title, objectives, discussion, conclusions)
Intervention flexibility	Considerations include posology, dose, dosing interval, windows allowed for dosing; permitted concomitant treatments. The domain is rated separately for experimental and comparisons treatment interventions
Medical practice setting/practitioner expertise	Considerations include experience, skills and resources of the practitioner and the treatment team; the healthcare delivery system; standards of care at the site, and local cultural practices that may influence medical delivery or outcomes. The domain is rated separately for experimental and comparisons treatment interventions.
Follow-up intensity and duration	Considerations include frequency and length of visits and the number and the scope of the assessments.
Outcome(s)	Considerations include evaluation of measure(s) by which the interventions' effects are assessed and how well they reflect outcomes that are used and considered important to real world practice.
Participant adherence	Considerations include the degree to which the subjects are encouraged and tracked for adherence to study-related procedures.

*Original domains, descriptors, and concept from Thorpe et al 2009 (see reference 1)

ASPECT-R (A Study Pragmatic-Explanatory Characterization Tool-Rating; ©2014 Janssen Pharmaceuticals, Inc.) has adapted ideas from these instruments to build a still more versatile instrument. The number of domains has been reduced to six that are specifically related to the explanatory-pragmatic spectrum. Domains identified as redundant and domains focused on measures of study quality have been eliminated. In addition, detailed definitions of terms and descriptive anchors have been developed to facilitate greater reliability across raters. The objective of this brief report is to describe the development of ASPECT-R and highlight some of its strengths and limitations.

ASPECT-R DOMAINS AND RATINGS

ASPECT-R consists of six domains deemed important for characterizing the explanatory to pragmatic spectrum of study designs. These six domains and their respective definitions are summarized in Table 1.

The ratings for each of the six domains range from 0 to 6, where,

in general, 0=extremely explanatory; 1=very explanatory; 2=explanatory; 3=elements of both designs; 4=pragmatic; 5=very pragmatic; and 6=extremely pragmatic. Specific, detailed descriptive anchors for each rating have been developed to guide the rater. The domains of Intervention Flexibility and Medical Practice Setting/Practitioner Expertise include separate ratings for the experimental and comparator intervention to account for differences in the relative pragmatic approach that may sometimes exist in these design elements. The experimental and comparison ratings of each of these two domains are averaged with the score plotted on the corresponding radar graph.

ASPECT-R EXCEL® FILE AND VISUALIZATION OF THE RATINGS

ASPECT-R is available as an Excel®-based file that contains nine worksheets (i.e., a cover worksheet page [Figure 1, Appendix 1]) and, as illustrated in Figures 2 through 9 (Appendix 1), one worksheet for each of the six domains (with two worksheets provided for the domains of Intervention Flexibility-Experimental and -Comparison; and two provided for Medical Practice Setting/Practitioner Expertise-Experimental and -Comparison]). The ASPECT-R rating for each of the domains is auto-populated on a radar graph that is embedded in each of the domain worksheet pages with the graph building as the rater completes each domain rating.

ASPECT-R RATERS EXPERTISE AND EXPERIENCE

Ideally, persons who use the ASPECT-R tool to rate studies have knowledge of and experience with designing clinical research studies. An advanced degree is not necessarily required to rate study domains; however, scoring of individual domains does require particular expertise regarding the study's population of interest, including its epidemiology and the clinical characteristics of the underlying illness/disorder, the course of the illness/disorder, general treatment regimens and modalities, as well as anticipated responses. Ideally, the rater has a broad understanding of treatment practices for the therapeutic area being examined.

The rater's ability to complete the tool in an accurate, reliable, and timely manner is also dependent upon their training and experience with respect to ASPECT-R, its appropriate application, and an understanding of the definitions of terms used. At a minimum the rater should review and understand the training materials that have been developed for the tool prior to completing an ASPECT-R rating. These materials include a training slide set, and the Rating Considerations and Rating Anchors embedded in the instrument itself.

SOURCE DOCUMENTS AND TIME REQUIREMENTS

Domain ratings for ASPECT-R are based upon the rater's review of the published manuscript and any additional information that reflects the study design and trial methodology. Other source documents that may be available and provide insight and information for the domain ratings include the study protocol and study report. These and other documents may be available on the clinical trials registration website (clinicaltrials.gov) or through other publicly available means. In some cases information may be best obtained through contact with the study authors and/or investigators themselves.

The cover page of the Excel® file for ASPECT-R provides cells for the rater to document the source documents utilized in determining the domain ratings, the particular study's objective, and the study population of interest. Completing these elements is a critical first step when conducting an ASPECT-R analysis, as these considerations will significantly impact the subsequent ratings assigned to each domain.

The individual ASPECT-R domain worksheets also contain a free-text cell for the rater to summarize the rationale for their score. This section should be used to document information from the study design that contributes to their ratings. The rater may also use this section to add personal knowledge of the study design. It is valuable to indicate here whether the study was part of a regulatory submission, as such trials require a high degree of rigor that likely contributes to the 'pragmaticness' of its design. Overall, documentation of the rationale for these ratings will facilitate better validity and reliability.

ASPECT-R generally takes approximately 30 to 60 minutes to complete for a given study; however, this may vary based upon the quality and clarity of the source documents, the rater's knowledge of the disease state and its management, and their familiarity with ASPECT-R.

DISCUSSION

Both explanatory and pragmatic study design approaches have value in the assessment of clinical interventions. Neither is considered intrinsically superior to the other. Indeed, many studies have both explanatory and pragmatic design characteristics. However, the increasing importance of real-world data for the provision of healthcare has driven the need for an increased understanding of the explanatory and pragmatic characteristics of clinical trials. For example, healthcare providers want to know if an intervention works in patients with concomitant medications and/or comorbid conditions (factors that often result in these individuals being excluded from explanatory studies). Such questions are often difficult to answer with traditional

explanatory studies that are designed to establish intervention or treatment efficacy under highly controlled scenarios and with selected patients.

A limitation to ASPECT-R at its current stage of development is that its use has largely been limited to the authors. To address its broader applicability, an inter-rater reliability validation study has been completed and accepted for publication.[3] In addition, completion of ASPECT-R can sometimes be limited by poorly documented or unavailable information regarding important features of study design such as site training and resources. The optimal application of ASPECT-R requires that users have considerable clinical trial expertise regarding the population of interest (e.g., schizophrenia) and its treatment (e.g., antipsychotic agents, psychotherapy). Another limitation to the findings from ASPECT-R is that it does not consider the quality of the study's design and conduct, or the validity of the interpretation of study's considering the development of a complementary ASPECT-type tool that will assess the clarity of the research question as well as the appropriateness of the study's design, procedures, conduct, analytical methods, and result interpretation.

In conclusion, ASPECT-R provides an improved descriptive approach for raters to consistently identify where a study's key design domains lie along the pragmatic to explanatory continuum. As such, ASPECT-R ratings should support the development of better pragmatic trial designs. They should also facilitate better understanding of a completed study's generalizability to real-world circumstances.

The complete ASPECT-R tool and guide materials can be accessed online by clicking or visiting this link: http://innovationscns.com/aspect-r-tool-and-training-materials/.

REFERENCES

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2. Tosh G, Soares-Weiser K, Adams CE. Pragmatic vs explanatory trials: the Pragmascope tool to help measure differences in protocols of mental health randomized controlled trials. *Dialogues Clin Neurosci*. 2011;13:209–215.
3. Bossie CA, Alphs LD, Williamson D, et al and the ASPECT-R Rater Team. Inter-rater reliability assessment of ASPECT-R—A Study Pragmatic-Explanatory Characterization Tool-Rating. *Innov Clin Neurosci*. 2016;13(3–4): In press. ■

APPENDIX 1. Figures 1–9: ASPECT-R worksheets

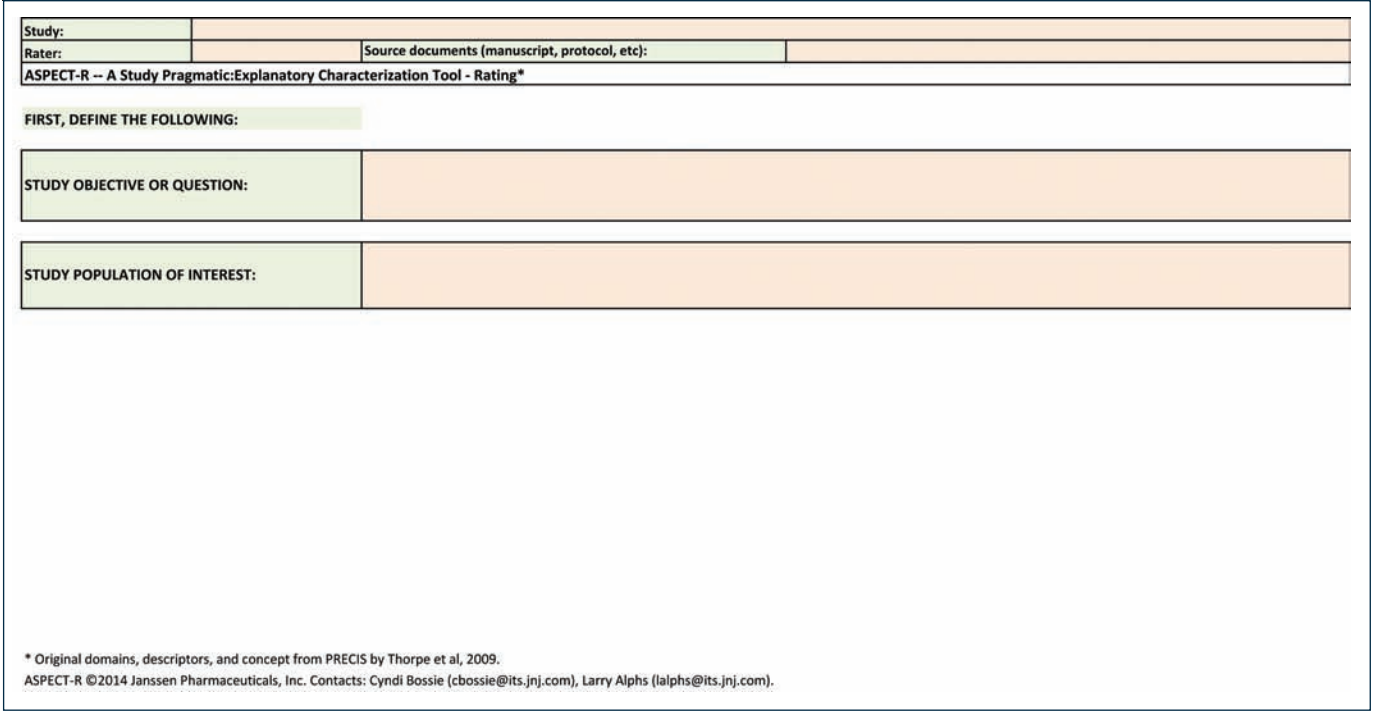
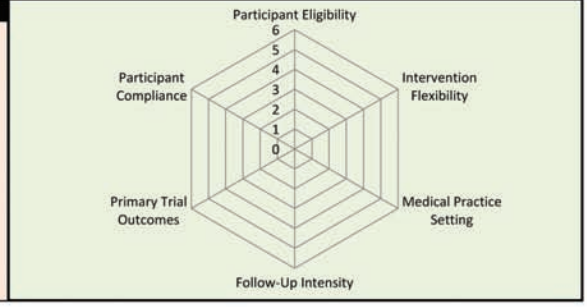


FIGURE 1. ASPECT-R—Defining the study objective and population of interest

Study:			
Rater:		Source documents (manuscript, protocol, etc):	

ASPECT-R -- A Study Pragmatic:Explanatory Characterization Tool - Rating*

Domain	Domain Description	Rating Considerations	Rating Anchors	Rating
1. Participant Eligibility Criteria	**Explanatory:** Selection criteria are applied that restrict study individuals to a defined and specific subgroup of the population of interest. **Pragmatic:** Individuals eligible for the study are fully representative of the population of interest.	• Consider to whom the reader is expected to generalize the result (ie, the intended treatment population). It is usually to persons with a defined disease/syndrome or a subpopulation of that disease/category. • Examine information provided in the title, stated objective(s), and conclusion(s) regarding the population of interest. • Determine if a "convenience" sample is used and, if so, how well it generalizes to the population of interest; note whether the sites selected for the study are representative of medical practice in the region of interest. • Consider inclusion / exclusion criteria that limit the generalizability of results relative to the population of interest. Consider restrictions on age, ICD diagnosis, symptom status, comorbidities, duration of illness, illness severity, prior treatments or hospitalizations, country, etc.	0 = Specific, protocol-mandated selection criteria for the eligible study population or non-random site selection restrict confident generalization of study results to 10% or less of the hypothesis-defined population of interest. 1 = Specific, protocol-mandated selection criteria for the eligible study population or non-random site selection restrict confident generalization of study results to >10% to ≤25% of the hypothesis-defined population of interest. 2 = Specific, protocol-mandated selection criteria for the eligible study population or non-random site selection restrict confident generalization of study results to >25% to <50% of the hypothesis-defined population of interest. 3 = Specific, protocol-mandated selection criteria for the eligible study population, or non-random site selection, restrict confident generalization to approximately 50% of the hypothesis-defined population of interest. 4 = Specific, protocol-mandated selection criteria for the eligible study population and site selection, allow confident generalization of study results to >50% to <75% of the hypothesis-defined population of interest. 5 = Specific, protocol-mandated selection criteria for the eligible study population and site selection, allow confident generalization of study results to 75% to <90% of the hypothesis-defined population of interest. 6 = Specific, protocol-mandated selection criteria for the eligible study population and site selection, allow confident generalization of study results to 90% or more of the hypothesis-defined population of interest.	

Rationale	
Free Text HERE	

* Original domains, descriptors, and concept from PRECIS by Thorpe et al, 2009.

FIGURE 2. Domain and domain descriptions and ratings for participant eligibility (Domain 1)

Study:				
Rater:		Source documents (manuscript, protocol, etc):		
ASPECT-R -- A Study Pragmatic:Explanatory Characterization Tool - Rating*				
Domain	Domain Description	Rating Considerations	Rating Anchors	Rating
2a. Intervention Flexibility - Experimental	**Explanatory:** Inflexible experimental intervention with strict instructions for every aspect of use. **Pragmatic:** Instructions on how to apply the experimental intervention are highly flexible, so as to reflect real world use and practice.	• Consider whether the study protocol assigns, mandates, or restricts the experimental intervention and aspects of its use beyond that of real world practice. • For a pharmacological intervention, consider instructions on: dose, when/how to increase or decrease dose, specific time of dosing, administration with or without food, interval between dosings, site for injection, or how to handle missed doses. • A chart review study would generally impose no restrictions on the intervention and, as such, reflects real world practice. • NOTE: Do NOT consider frequency and timing of study assessments here. These are considered in Domain 4: "Follow-up intensity/Duration."	0 = Use of the experimental intervention is carefully and precisely defined for nearly all aspects of its use in the study. 1 = Use of the experimental intervention is carefully and precisely defined for most aspects of its use in the study. 2 = Use of the experimental intervention is defined such that many aspects of its use are constrained by the study protocol. Use is somewhat more constrained than that outlined in existing (or anticipated) product label. 3 = Use of the experimental intervention is defined such that restrictions are limited to the constraints of the existing (or anticipated) product label, or to constraints of another standardized and broadly used definition for the use of the intervention. 4 = Use of the experimental intervention is defined such that it allows for limited use beyond the constraints of the existing (or anticipated) product label or beyond that of another standardized definition of the intervention. 5 = Use of the experimental intervention is defined such that it allows for considerable use beyond the constraints of the existing (or anticipated) product label or another standardized definition of the intervention. Minimal constraints remain. 6 = Use of the experimental intervention is limited only by considerations of what the practitioner personally considers to be ethical and good clinical practice.	
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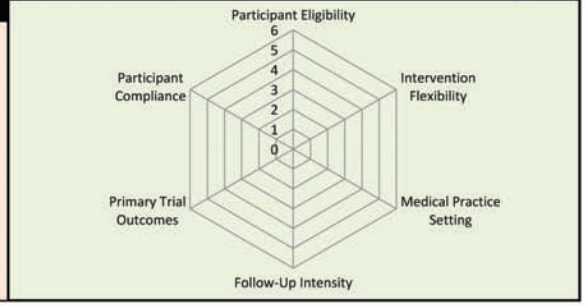
Free Text HERE				

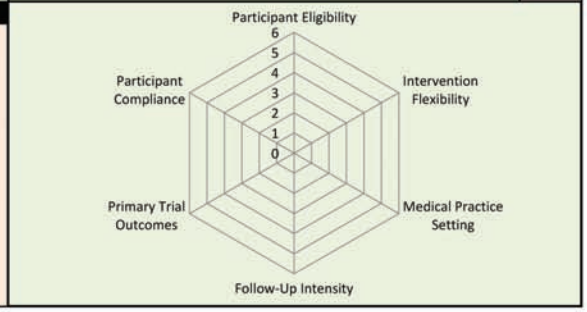
* Original domains, descriptors, and concept from PRECIS by Thorpe et al, 2009.

FIGURE 3. Domain and domain descriptions and ratings for intervention flexibility-experimental (Domain 2a)

Study:			
Rater:		Source documents (manuscript, protocol, etc):	

ASPECT-R -- A Study Pragmatic:Explanatory Characterization Tool - Rating*

Domain	Domain Description	Rating Considerations	Rating Anchors	Rating
2b. Intervention Flexibility - Comparison	**Explanatory:** Inflexible comparison intervention with strict instructions for every aspect of use. **Pragmatic**: Instructions on how to apply the comparison intervention are highly flexible, so as to reflect real world use and practice.	• Consider whether the study protocol assigns, mandates, or restricts the comparison intervention and aspects of its use beyond that of real world practice. • For a pharmacological intervention, consider instructions on: dose, when/how to increase or decrease dose, specific time of dosing, administration with or without food, interval between dosings, site for injection, or how to handle missed doses. • Consider whether the comparator is placebo instead of the best alternative active comparator. • A chart review study would generally impose no restrictions on the intervention and, as such, reflect real world practice. • NOTE: Do NOT consider frequency and timing of study assessments here. These are considered in Domain 4: "Follow-up intensity/Duration."	0 = Use of the comparison intervention is carefully and precisely defined for nearly all aspects of its use in the study. 1 = Use of the comparison intervention is carefully and precisely defined for most aspects of its use in the study. 2 = Use of the comparison intervention is defined such that many aspects of its use are constrained by the study protocol. Use is somewhat more constrained than that outlined in existing (or anticipated) product label. 3 = Use of the comparison intervention is defined such that restrictions are limited to the constraints of the existing (or anticipated) product label, or to constraints of another standardized and broadly used definition for the use of the intervention. 4 = Use of the comparison intervention is defined such that it allows for limited use beyond the constraints of the existing (or anticipated) product label or beyond that of another standardized definition of the intervention. 5 = Use of the comparison intervention is defined such that it allows for considerable use beyond the constraints of the existing (or anticipated) product label or another standardized definition of the intervention. Minimal constraints remain. 6 = Use of the comparison intervention is limited only by considerations of what the practitioner personally considers to be ethical and good clinical practice.	

Rationale	
Free Text HERE	

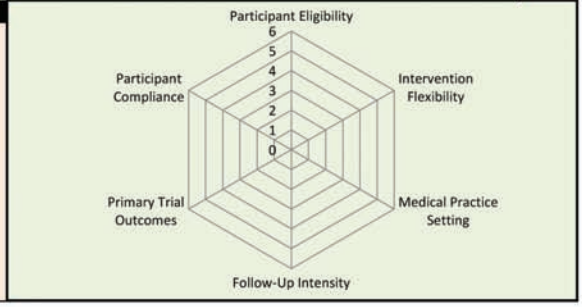
* Original domains, descriptors, and concept from PRECIS by Thorpe et al, 2009.

FIGURE 4. Domain and domain descriptions and ratings for intervention flexibility-comparison (Domain 2b)

Study:			
Rater:		Source documents (manuscript, protocol, etc):	

ASPECT-R -- A Study Pragmatic:Explanatory Characterization Tool - Rating*

Domain	Domain Description	Rating Considerations	Rating Anchors	Rating
3a. Medical Practice Setting / Practitioner Expertise - Experimental	**Explanatory:** The experimental intervention is applied only by seasoned practitioners in the field of interest, and in practice settings where the care delivery system and providers are highly experienced in managing the types of patients enrolled in the trial. **Pragmatic**: The full range of practitioners in the full range of clinical settings are eligible to participate in the trial.	• Consider the range of practitioners relative to their: skill sets, training regarding use of the intervention, specialized training for ratings or other research procedures, requirements for special certifications, and experience or specialized skills with the intervention or research activities. • Consider the standard of medical care provided by study practitioners and the expertise of staff at the site/setting where the study has been conducted relative to that available to all patients included in the population of interest.	0 = Practitioners in the study are limited to those with very well defined or implied skill sets that are held by very few practitioners in the real world who might ever use the experimental intervention. Extensive study-specific training or expertise is required to qualify as an investigator for the trial. 1 = Practitioners in the study are limited to those with very well defined or implied skill sets that are held by a small number of practitioners in the real world who might ever use the experimental intervention. Substantial specialized study-specific training or expertise is required to qualify as an investigator for the trial. 2 = Practitioners in the study are limited to those with very well defined or implied skill sets that are held by a meaningful proportion (but less than half) of practitioners in the real world who might ever use the experimental intervention. Some study-specific training or expertise is required to qualify as an investigator for the trial. 3 = Practitioners in the study are limited to those with skill sets that are held by about half of all practitioners in the real world who might ever use the experimental intervention, but not by a sizeable subgroup. Some study-specific training or expertise is required to qualify as an investigator for the trial. 4 = Practitioners in the study are those with skill sets that are held by a substantial proportion (more than half) of practitioners in the real world who might ever use the experimental intervention. Little to no study-specific training or expertise is required to qualify as an investigator for the trial. 5 = Practitioners included in the study are those with skill sets that are held by most practitioners in the real world who might ever use the experimental intervention. Little to no study-specific training or expertise is required to qualify as an investigator for the trial. 6 = Practitioners included in the study are those with skill sets that are held by all or nearly all practitioners in the real world who might ever possibly use the experimental intervention. No study-specific training or expertise is required to qualify as an investigator for the trial.	

Rationale	
Free Text HERE	

* Original domains, descriptors, and concept from PRECIS by Thorpe et al, 2009.

FIGURE 5. Domain and domain descriptions and ratings for medical practice setting/practitioner expertise-experimental (Domain 3a)

Study:			
Rater:		Source documents (manuscript, protocol, etc):	

ASPECT-R -- A Study Pragmatic:Explanatory Characterization Tool - Rating*

Domain	Domain Description	Rating Considerations	Rating Anchors	Rating
3b. Medical Practice Setting / Practitioner Expertise - Comparison	**Explanatory:** The comparator intervention is applied only by seasoned practitioners in the field of interest, and in practice settings where the care delivery system and providers are highly experienced in managing the types of patients enrolled in the trial. **Pragmatic:** The full range of practitioners in the full range of clinical settings are eligible to participate in the trial.	• Consider the range of practitioners relative to their: skill sets, training regarding use of the intervention, specialized training for ratings or other research procedures, requirements for special certifications, and experience or specialized skills with the intervention or research activities. • Consider the standard of medical care provided by study practitioners and the expertise of staff at the site/setting where the study has been conducted relative to that available to all patients included in the population of interest.	0 = Practitioners in the study are limited to those with very well defined or implied skill sets that are held by very few practitioners in the real world who might ever use the comparator intervention. Extensive study-specific training or expertise is required to qualify as an investigator for the trial. 1 = Practitioners in the study are limited to those with very well defined or implied skill sets that are held by a small number of practitioners in the real world who might ever use the comparator intervention. Substantial specialized study-specific training or expertise is required to qualify as an investigator for the trial. 2 = Practitioners in the study are limited to those with very well defined or implied skill sets that are held by a meaningful proportion (but less than half) of practitioners in the real world who might ever use the comparator intervention. Some study-specific training or expertise is required to qualify as an investigator for the trial. 3 = Practitioners in the study are limited to those with skill sets that are held by about half of all practitioners in the real world who might ever use the comparator intervention, but not by a sizeable subgroup. Some study-specific training or expertise is required to qualify as an investigator for the trial. 4 = Practitioners in the study are those with skill sets that are held by a substantial proportion (more than half) of practitioners in the real world who might ever use the comparator intervention. Little to no study-specific training or expertise is required to qualify as an investigator for the trial. 5 = Practitioners included in the study are those with skill sets that are held by most practitioners in the real world who might ever use the comparator intervention. Little to no study-specific training or expertise is required to qualify as an investigator for the trial. 6 = Practitioners included in the study are those with skill sets that are held by all or nearly all practitioners in the real world who might ever possibly use the comparator intervention. No study-specific training or expertise is required to qualify as an investigator for the trial.	

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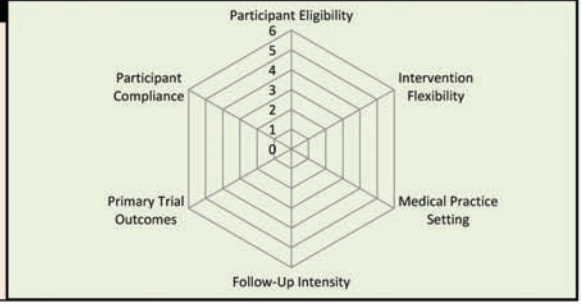
Free Text HERE	

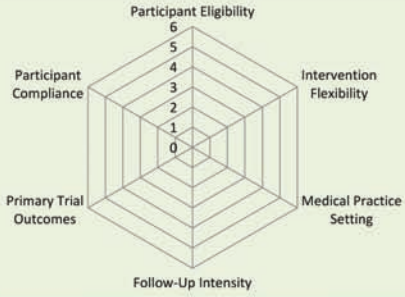
* Original domains, descriptors, and concept from PRECIS by Thorpe et al, 2009.

FIGURE 6. Domain and domain descriptions and ratings for medical practice setting/practitioner expertise-comparison (Domain 3b)

Study:			
Rater:		Source documents (manuscript, protocol, etc):	

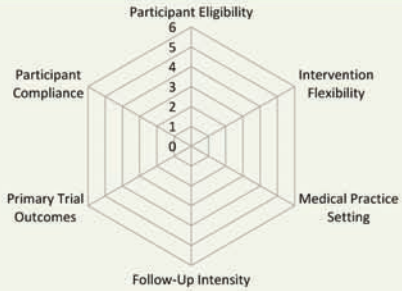
ASPECT-R -- A Study Pragmatic:Explanatory Characterization Tool - Rating*

Domain	Domain Description	Rating Considerations	Rating Anchors	Rating
4. Follow-up Intensity / Duration	**Explanatory:** Study participants are followed with more frequent visits and more extensive data collection than would occur in clinical practice, regardless of their clinical need. **Pragmatic**: Follow-up is limited to usual clinical practice.	• Consider the protocol-defined visit frequency, structure, time commitment and/or intensity of contact. • Consider the number of interventions and assessments required to complete the evaluation and the time necessary to complete them (ie, specialized tests, rating scales, additional therapies, etc.) relative to what is available in standard practice. • Consider the invasiveness of the intervention relative to that used in standard practice, ie, requirements for pharmacokinetic sampling, magnetic resonance imaging, hospitalization.	0 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are very explicitly and precisely defined by the study protocol. These visit parameters are much greater than those which would be seen in normal clinical practice. 1 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are explicitly defined and go considerably beyond those outlined in available treatment guidelines or standard practice. 2 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are defined such that they are more constrained than those outlined in available treatment guidelines or standard practice. 3 = Some elements of the visit frequency/structure/duration/intensity or the duration of the study, but not all, are more constrained than those outlined in available treatment guidelines or standard practice. 4 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are defined such that they conform to available treatment guidelines or standard practice. 5 = Visit frequency/structure/duration/intensity, as well as the duration of the study, are defined such that flexibility is allowed beyond that found in available treatment guidelines or standard practice. 6 = No constraints are put on visit frequency/structure/duration/intensity or follow-up period.	

Rationale	
Free Text HERE	

* Original domains, descriptors, and concept from PRECIS by Thorpe et al, 2009.

FIGURE 7. Domain and domain descriptions and ratings for follow-up intensity/duration (Domain 4)

Study:				
Rater:		Source documents (manuscript, protocol, etc):		
ASPECT-R -- A Study Pragmatic:Explanatory Characterization Tool - Rating*				
Domain	Domain Description	Rating Considerations	Rating Anchors	Rating
5. Primary Trial Outcomes	**Explanatory:** The outcome is known to be a direct and immediate consequence of the intervention. Its relationship to an important clinical outcome has not been established. The outcome may require specialized training or testing not normally used in general clinical practice. **Pragmatic**: The primary outcome is an objectively measured, clinically meaningful outcome to the study participants. It does not rely on central adjudication, is one that can be assessed under usual conditions, and does not require special training or tests beyond those used in general clinical practice.	• Consider that more explanatory outcome measures may require specialized training to complete an adequate assessment. It may be necessary to complete such assessments in specialized settings with specialized instrumentation or personnel who have unique skill sets (eg, ability to assess persons on specialized symptom scales). Information generated from them may be important for the driving question of the clinical trial, but has limited value as an outcome in general clinical practice (eg, measurement of brain cortical volume in a depression trial). • Consider that more pragmatic outcome measures are clinically obvious and generally accepted as clinically important, such as hospitalization or death. • Consider all trial outcomes that support the primary study question, giving the most weight to those predefined as the study primary endpoint. • Scales used to assess outcomes should be evaluated with regard to how informative they are to clinical practice. Surrogate markers of clinical response, like a triglyceride level, would be considered more explanatory. Measures of death or all cause hospitalization would be considered more pragmatic. A total score on a scale measuring psychosis would be intermediate. • Consider how much the outcomes are influenced by the treatment settings or systems of care used in the study and whether they can be easily generalized to customary clinical practice.	0 = In the aggregate, trial outcome measures support an overall result for which no direct link to a clinically important outcome has been established. 1 = In the aggregate, trial outcome measures support an overall result for which only a very limited link to a clinically important outcome has been established. 2 = In the aggregate, trial outcome measures support an overall result for which only a limited link to a clinically important outcome has been established. 3 = In the aggregate, trial outcome measures support an overall result that represents an established outcome, but one which requires extrapolation regarding its clinical importance. 4 = In the aggregate, trial outcome measures support an overall result that represents a well-established clinical outcome requiring moderate interpretation regarding its clinical importance. 5 = In the aggregate, trial outcome measures support an overall result that represents a well-established clinical outcome requiring limited interpretation regarding its clinical importance. 6 = In the aggregate, trial outcome measures support an overall result that represents a well-established and important clinical outcome requiring no complex interpretation.	
Rationale				
Free Text HERE				

* Original domains, descriptors, and concept from PRECIS by Thorpe et al, 2009.

FIGURE 8. Domain and domain descriptions and ratings for primary trial outcomes (Domain 5)

Study:				
Rater:		Source documents (manuscript, protocol, etc):		
ASPECT-R -- A Study Pragmatic:Explanatory Characterization Tool - Rating*				
Domain	Domain Description	Rating Considerations	Rating Anchors	Rating
6. Participant Compliance	**Explanatory:** Study participants compliance with the intervention is monitored closely, may be a pre-requisite for study entry, and both prophylactic and rescue strategies are used. **Pragmatic:** There is unobtrusive or no measurement of compliance, and no strategies for rescue beyond normal clinical practice.	• Consider study protocol directives that assure participant compliance with the intervention. • Protocol directives to consider include: protocol-defined observation of the compliance with the intervention, use of blood drug levels, patient report via interview, patient diary, caregiver report via interview, caregiver support, pill counts, documentation, or if no relevant information is gathered. • Consider that retention efforts will likely have an effect on compliance. • Consider protocol mandates disallowing or requiring co-therapeutic interventions in each arm. • Consider that requirements for informed consent can correspond to a protocol directive that may impact compliance (rating of 4 or lower).	0 = Protocol directives exist such that participant compliance with the intervention is required to continue in the study. This is confirmed and well documented. Patients are excluded for non-compliance. 1 = Protocol directives exist such that participant compliance with the intervention is strongly encouraged and documented, but not required in order to continue in the study. 2 = Protocol directives exist such that participant compliance with the intervention is strongly encouraged and documented. 3 = Protocol directives exist such that participant compliance with the intervention is strongly encouraged; documentation of compliance is not required. 4 = Some protocol directives exist that may impact participant compliance with the intervention; documentation of compliance is not required. 5 = Few protocol directives exist that may impact participant compliance with the intervention; documentation of compliance is not required. 6 = No protocol directives exist to assure or document participant compliance with the intervention.	
Rationale				
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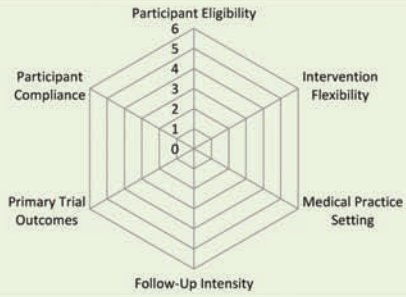

* Original domains, descriptors, and concept from PRECIS by Thorpe et al, 2009.

FIGURE 9. Domain and domain descriptions and ratings for participant compliance (Domain 6)