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Use of Patient Reported Outcomes for Substantiation of Structure Function Claims

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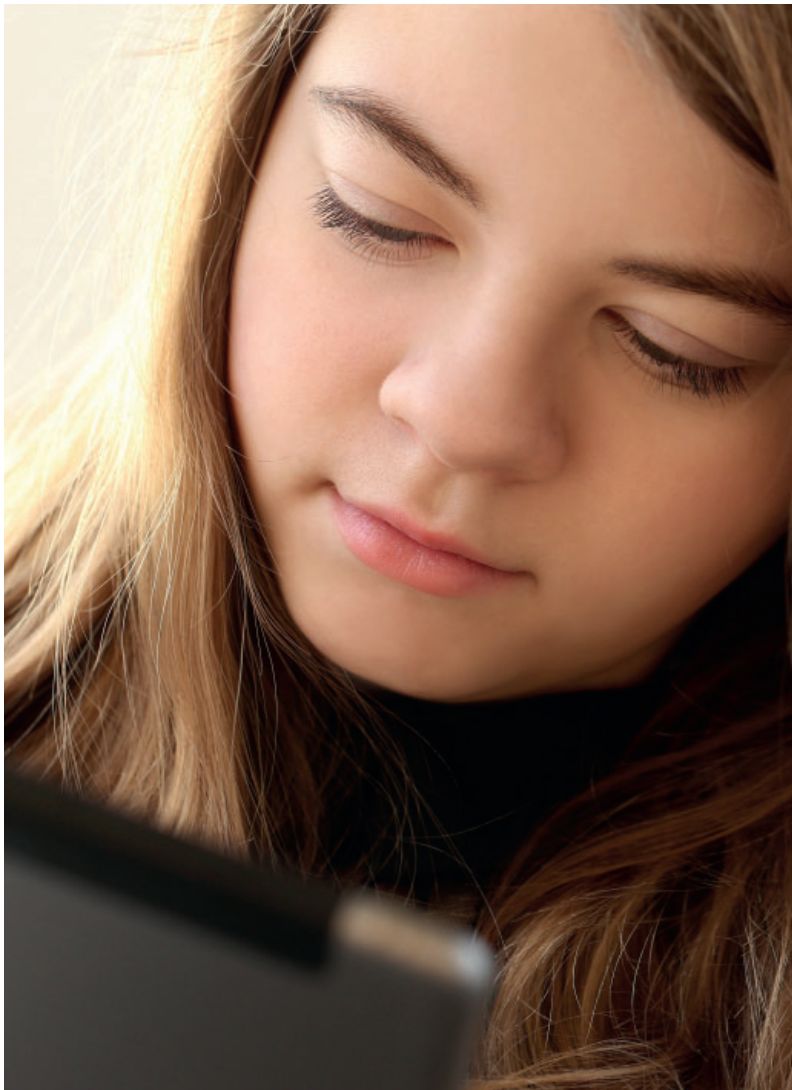
Patient Reported Outcomes Research to Support Claims on Food Products

Walk the halls of the largest trade shows in the industry or meander just outside hotel conference rooms in dim lit bar seating at your next break-out session, and you are likely to hear about the latest buzz in the industry. The buzz over the past 2 years in the clinical trial world has involved the ever-expanding use of consumer surveys and questionnaires, known as Patient Reported Outcome instruments, to substantiation claims on food products. In particular, the latest talk from the nutraceutical/dietary supplement echo chamber at trade shows has centered around use of the Patient Reported Outcomes Measurement Information System (PROMIS), a 10-year effort spearheaded by the National Institutes of Health (NIH). The 10-year program was intended "to develop an efficient state-of-the-art assessment system for self-reported health. The program developed next generation patient-reported outcome (PRO) measures using large item banks and computerized adaptive testing, which allowed for well-organized and effective assessment of PRO in clinical research in a wide variety of chronic diseases." The second phase of PROMIS studies (PROMIS II), funded from 2009-2014, continued the agenda of PROMIS I (2004-2009) with an increased emphasis on pediatric populations. Today, PROMIS is a publicly available system of patient-reported health status for physical, mental, and social well-being that can be used to measure health symptoms and health-related quality of life domains such as pain, fatigue, depression, and physical function, which are relevant to a variety of chronic diseases, including cancer. Today the PROMIS network contains questionnaire surveys for over 70 domains measuring pain, fatigue, depression, anxiety, sleep disturbance, physical function, social function, and sexual function just to name a few. It is also relatively inexpensive to employ in a clinical trial as a tool for substantiating claims. Are Patient-Reported Outcomes new to the contract research organization (CRO) community? Are use of PROs alone too good to be true? Can they provide complete objective substantiation by themselves for product marketing claims? Is it a complimentary tool that requires additional data to support a claim? Or is it the latest ball of yarn distraction for the industry to pursue until the next one comes along?

What Can One Achieve with PROs?

This white paper will discuss use of patient reported outcomes or PROs in clinical trials to evaluate dietary supplement and food products for non-disease conditions. A PRO is any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy. PROs provide a unique approach because some effects of a health condition and its therapy are known only to patients. The key is whether the PRO is fit for purpose (i.e., properly developed and evaluated).



What is a PRO Instrument?

Patient-reported outcomes are nothing new to CROs. We use them as part of our clinical trials. PRO instruments are tools typically in the form of questionnaires (plus the information and documentation that support its use) designed to capture PRO data used to measure treatment benefit or adverse event risks in clinical trials. A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. The outcome can be measured and scored as a one-time snapshot event, including a severity of a symptom or state of disease or as a change over time from a previous measure. In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts, such as a symptom or groups of symptoms, effects on a particular function or group of functions, or a group of symptoms or functions shown to measure the severity of a health condition.

How are PRO Instruments used today in drug research?

Patient-reported outcomes and their instruments (e.g., questionnaires to be completed by trial participants) are used in clinical trials to assess how a patient feels. PRO instruments used in drug trials are almost exclusively aimed at comparing the SIDE EFFECTS experienced by the patient between the test drug article and a known earlier generation drug that has been on the market. Trials sponsored by university and research organizations were more likely to measure PRO than the major sponsor types of drugs (commercial firms and NIH). In a study of 17,704 intervention trials between 2004 and 2007, only 14% of trials included a PRO. PRO use in clinical trials are typically only seen in behavior interventions (e.g., the patient's feeling and response is important in the overall assessment), procedure interventions, and device interventions in comparison to drug interventions.

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Can PRO instruments be used to support medical product labeling?

Yes, findings measured by a well-defined, validated, and reliable PRO instrument in appropriately designed investigations can be used to support a claim in medical product labeling if the claim is consistent with the instrument's documented measurement capability. Use of a PRO instrument is advised when measuring a concept best known and understood by the patient or best measured from the patient's perspective. A PRO instrument, like physician-based instruments or laboratory biomarkers followed for monitoring disease status, should be shown to measure the concept it is intended to measure. The 'concepts' measured by PRO instruments that are most often used in support of labeling claims refer to a patient's symptoms, signs, or an aspect of functioning directly related to disease status. PRO measures often represent the effect of disease on health and functioning from the patient perspective. These PRO-substantiated claims, to give them their own terminology, generally appear in either the "Indications and Usage" or "Clinical Studies" section of labeling but can theoretically appear in any section.

The effects of prescription drugs can be characterized by more than additional safety and efficacy parameters. While clinically meaningful end points are needed to understand a drug's usefulness and benefit as a safe and effective therapy, the impact of a drug on a variety of parameters, including lifestyle, work style and personal and quality-of-life outcomes, has become an important component for characterizing the effects of a drug. To make PRO claims in advertising and labeling of pharmaceuticals, companies and FDA must decide if the claims are truthful and in any way false or misleading. So how much support is actually necessary if a drug has already been demonstrated to be safe and effective on primary efficacy measures described in the product's indications? What is the nature and amount of additional evidence needed to demonstrate support for claims that are already logically consistent with the clinically meaningful outcomes ascribed to the product's indications? FDA's response seems to be that considerable evidence is required.

What Actions Has FDA Taken Regarding PRO Claims Made in Advertising?

FDA has taken numerous companies to task over quality of life and other PRO Claims, and the overall trends are quite obvious. In one letter, a manufacturer described the disabling effects of IBS in terms of health-related quality of life, economic costs, and worker productivity. FDA cited these PRO claims as unsubstantiated because the use of such burden of illness claims in conjunction with promotional material about the product implied that it would improve these outcomes, which was unsubstantiated. In another letter, a product used for osteoporosis was described as "preserving your independent lifestyle"; however, this PRO claim was branded as misleading because it implied an outcome (primary) that had not been demonstrated by substantial evidence. In another letter, FDA objected to claims that a product affected quality of life issues plaguing participants in their ability to work or manage a home, restricted recreational activities, limited personal and/or social relationship, physical and emotional effects. FDA called these claims out as misleading because the product was never shown to have an effect on physical, mental and social functioning with substantial evidence. Even with claims to "get back to your life sooner", FDA regulated the statements as unsubstantiated claims for improved functional status and productivity. One letter cited a potent pain reliever patch making quality of life claims that it required substantial supporting evidence in the form of adequate and well-controlled studies designed to specifically address these outcomes. So, we can certainly say you need to substantiate quality of life claims and not doing so will land you in great regulatory peril. How about the case where you substantiate quality of life and other PRO claims but fail to address primary outcomes through changes in biomarkers and physiological parameters? Drug companies would not do this, but is it a strategically viable path for a dietary supplement company? This is the latest rage in the dietary supplement world at present, and to examine it more closely we will need to get off of the regulatory astro-turf and into the grass and weeds on the issue.

Is a Clinical Trial Involving a PRO-Assessment Useful in Comparison to a Clinical Trial with Physiologic Endpoints?

PRO-Assessment of Clinical Signs/Symptoms in Combination with Physiologic Endpoints

Any assessment in a clinical trial can be useful relatively speaking. It all depends on what you are trying to accomplish from the clinical study. Let's take the typical clinical trial where you are assessing a physiologic effect from some sort of biomarker evaluated over the time course of the study. For example, one could have a vigorous exercise study aimed at the ability of a test article to reduce inflammation and occasional pain after such vigorous exercise. In such a study, one might examine inflammation using the biomarkers C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). In addition, one might add a PRO-assessment to monitor patient reported symptoms of the disease such as assessment of joint discomfort, pain and/or some other quality of life assessment. In this case, the clinical trial would need to succeed on the biomarkers, which are clinically used to monitor inflammation, before success could be attained on the secondary endpoints (see Figure 1.)

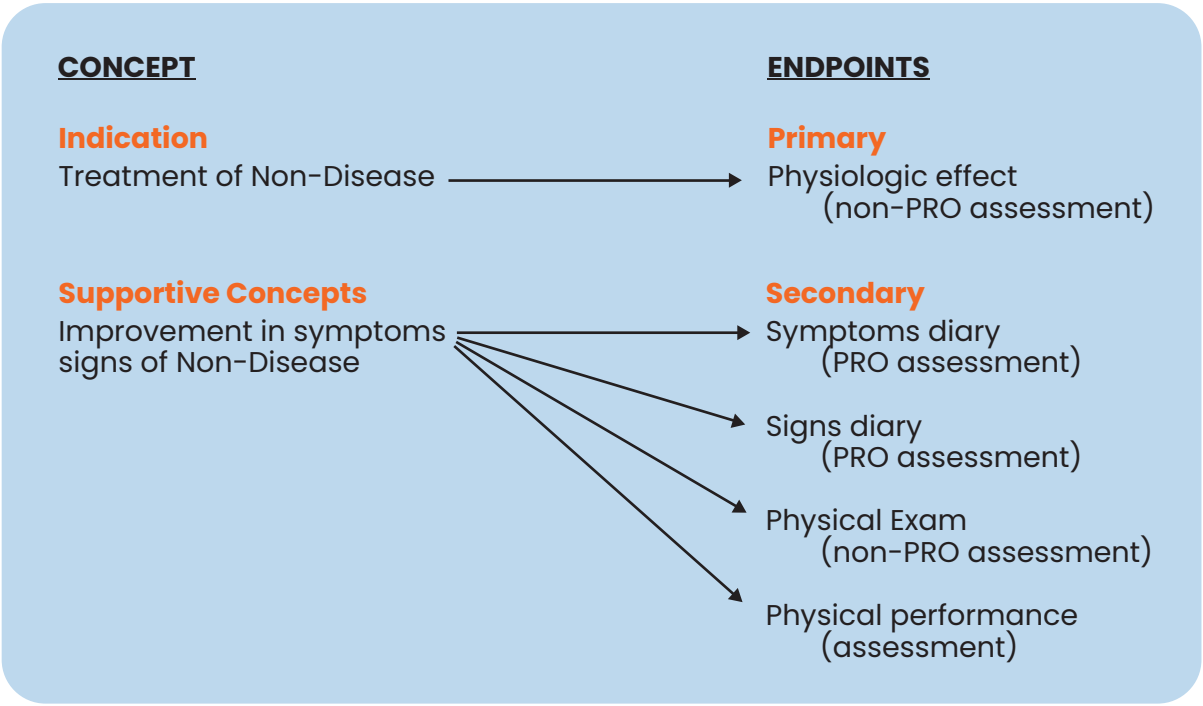

Figure 1. Supporting/treating occasional inflammation/pain after routine vigorous exercise.

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Is a Clinical Trial Involving a PRO-Assessment Useful in Comparison to a Clinical Trial with Physiologic Endpoints?

A second option might be using a PRO-symptom assessment as the primary clinical trial endpoint intended to support an indication for the treatment of symptoms associated with a non-disease structure function claim such as occasional inflammation/pain after vigorous exercise. In this scenario, secondary endpoints to evaluate physical performance and/or limitation measures would be critical (see Figure 2). The physical endpoint could be accomplished either through an objective evaluation of physical performance in a task or as another PRO-assessment. In other words, relying on the patient reported (subjective) feeling that inflammation or pain has improved would not alone be enough. One would still need an objective physiologic evaluation of physical performance involving the joint. Only together could positive results support a generalized, claim to provide occasional joint pain and inflammation relief after vigorous exercise (e.g., running a marathon). If one only completed a PROMIS instrument questionnaire as the clinical trial design and it was statistically significant, the permissible structure function claim would be much more limited in scope to "helps with the perception of occasional pain".

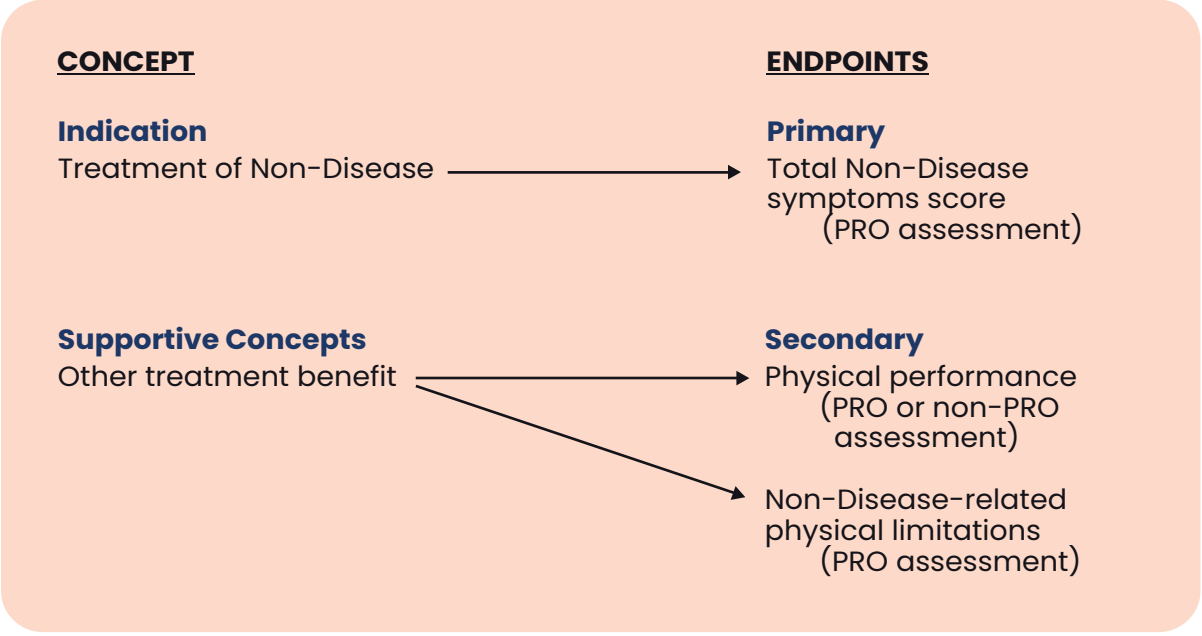

Figure 2. Clinical trial scheme for treatment of symptoms associated with a non-disease.

Versatility and Limitations of Patient Reported Outcome Measures in PROMIS®

It is not a surprise that PROs and PRO instruments are on the rise in clinical trials. Use of PRO instruments has gained considerable traction in the dietary supplement industry over the past year. KGK has used PRO instruments in dietary supplement trials, but how useful are they to substantiating structure function claims? Table 1 below summarizes all of the PROMIS® adult measures for research domains provided by NIH. All of these questionnaires are subjective responses on the part of the participant. While they may be 'validated', their utility in providing substantiation for a structure function claim is dependent upon they are incorporated into the trial design. They are primarily used for evaluating the side effects of drug treatments, behavior interventions, procedure interventions and device interventions. None of the research domains listed below are based upon objective outcomes such as biomarkers and objective physiological assessments by physicians. In other words, use of pain questionnaires as PROMIS instruments would only speak to whether a participant feels like the pain intensity is less. This is why PROMIS instruments have been adopted to evaluate side effects from using drugs as a way to compare those effects to a first or earlier generation therapeutic involving the same mechanism of action. A pain questionnaire

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Versatility and Limitations of Patient Reported Outcome Measures in PROMIS®

would not provide incontrovertible proof that pain is somehow minimized, range of motion has recovered and therefore the product helps consumers to restore their physical activity once again. A PROMIS instrument for pain only assesses the participant's subjective feeling or belief about their pain. PROMIS instruments are geared more toward the evaluation of side effects from use of therapeutics as test articles in clinical trials.

Another analogy to illustrate this point comes from the cosmetic industry where firms are not permitted to make claims for cosmetic products related to structure or function. On cosmetic products we see claims of the type: "makes the skin look smooth and less wrinkly". This is a subjective claim and offers nothing as to whether the product objectively causes the skin to exhibit fewer wrinkles. Another example of a permissible cosmetic claim is how the product "makes the skin feel cooler". Similarly, dietary supplement claims based upon PROMIS questionnaires are subjective and should be qualified and limited in scope to the personal inner experience related to consumption of the dietary supplement test article in the clinical trial.

The most useful PROMIS instruments for dietary supplements are in the area of quality-of-life claims upon ingestion of the test article. Whatever PROMIS instrument one chooses for their dietary supplement clinical trial, the design should account for both subjective and objective findings in the study. Claims based upon statistically significant questionnaire results in a clinical trial using only PROMIS instruments should be limited in scope to the subjective feelings of the participant's overall experience. And again, those subjective PROMIS-based claims are more akin to the cosmetic industry than ones expected by consumers for dietary supplements.

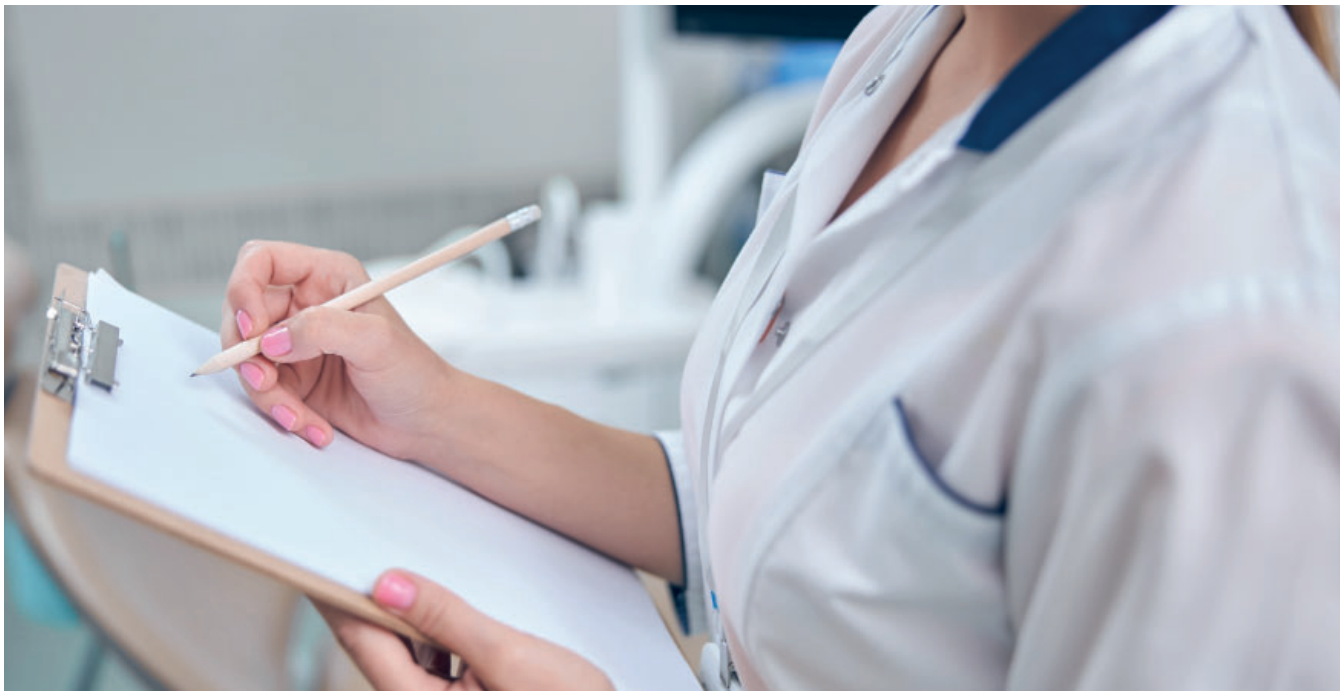
PROMIS Adult Measures for Research Domains

Research Domain	What is Measured
Global Health	Overall general evaluation of one's physical and mental health
Global Mental Health	Overall evaluation of one's mental wellbeing
Global Physical	Overall evaluation of one's physical wellbeing
Alcohol Related	Drinking patterns, cue-based drinking, cravings to drink
Cognitive Function	Mental acuity, concentration, memory, perceived changes in cognitive functions.
Emotion	Anger, Anxiety, fear, depression, loneliness, social cognition, etc.
General Life Satisfaction	One's cognitive evaluation of life experiences and personal satisfaction with their life
Meaning and Purpose	Evaluation of feelings that one's life is worthy, hopeful, reason for living
Attitudes	Positive Affect, Psychosocial illness Impacts, Self-Efficacy (perceptions over being able to deal with stressful situations)
Smoking	Improved cognition, coping strategies
Substance Use	Appeal, Rx Misuse, Severity
Dyspnea	Activity motivation, Activity requirements, environmental factors, assistive device use, characteristics, intensity of shortness of breath, emotional response, task avoidance, time extension, severity
Fatigue	Cancer fatigue
Gastrointestinal	Belly pain, bowel incontinence, constipation, diarrhea, disrupted swallowing, gas/bloating, reflux, nausea/vomiting
Pruritis	Activity/clothing, mood/sleep, interference with quality of life, quality of life impairment, severity, triggers, and behavior
Pain	Evaluate how pain affects other aspects of one's life (social, cognitive, emotional, physical, recreational activities), pain intensity, quality of neuropathic pain, nociceptive pain
Physical Function	Only self-reported capability rather than actual performance of physical activity, self-reported assessment of mobility, self-reported assessment of upper extremity
Sexual Function and Satisfaction	Extent to which people self-report being bothered by aspects of sexual function, maintaining erection, symptoms of disease, side effects of treatment, etc.
Sleep	Self-reported disturbance in perceptions of sleep quality, sleep depth, and restoration associated with sleep, sleep-related impairment in alertness
Social Health	Perceived ability to perform one's usual social roles and activities, companionship, emotional support, informational support, instrumental support (requiring assistance with material, cognitive or task performance), social isolation
Various Profiles	Multi-Domain Questionnaires Developed

Table 1. PROMIS Adult Measures for Research Domains

Additional Benefits of Doing Clinical Trials Outside of the Completely Virtual Model
Using PROMIS Questionnaires

One of the most obvious advantages of doing clinical research in person, as compared to completely remote studies, is the assurance that study participants understand their role, responsibilities, and rights in the research, and that the clinical trial staff are regularly assessing and supporting the participant in their compliance with study procedures. One of the greatest challenges of completely remote studies is effective vetting of and communication with study participants. Not only is there an ethical imperative to ensure that study participants understand their role and any risks involved with participation, the reliability of the research and the safety of the study participants requires effective communication. IRBs require that the study procedures, risks, and rights be communicated with a participant to ensure their understanding, which generally requires direct contact between the study staff and the participant either in-person or through tele- or video conference. The participant must also have an effective means to report adverse events throughout their participation. To ensure that the data collected is reliable, compliance in taking the investigational product and completing the study assessments should be regularly assessed.



The advent of digital health tools has afforded researchers the ability to collect data remotely and utilize electronic signatures to verify study records. While this facilitates a low-cost option for data collection from a large and diverse population of participants, sometimes you get what you pay for. Improper use of these tools, the use of inappropriate tools, or simply a lack of engagement from the investigating researchers, can lead to a study that is rife with low compliance, missing data, and high dropout rates and may even pose risks associated with data security or ineffective oversight over the study. Effective study procedures should be in place to ensure that participants are engaged in the study and that their compliance with completing study questionnaires, food records, diaries is assessed on a regular basis throughout the participation of each study participant. Investigational product packaging should be mailed back to the study site so that a physical count to verify compliance can take place. Traditional in-person clinical trials conducted by qualified personnel have an advantage here in that they can provide greater assurance of a high-quality study, but a remote clinical trial can still be conducted effectively and provide valuable scientific information if conducted rigorously. It is imperative for prospective sponsors to do their due diligence to ensure that their study is conducted with adequate controls and assessments, and most importantly, according to ethical standards of human research to ensure that they are not paying for a study that lacks integrity.

Conclusions

The growth in PRO instrument usage in clinical trials is not surprising. The development of expensive therapeutics intended for serious illnesses that extend life but may introduce significant adverse side effects, has created a greater need for PRO assessments in clinical trials. PRO instruments are typically used by non-commercial organizations and most often in the area of quality-of-life questionnaires for cancer treatments. PROMIS instruments are typically used in clinical trials for behavior interventions, procedure interventions, and device interventions. When used in the drug industry, PROMIS instruments are used to evaluate side effects experienced by participants when using those drug treatments and not as primary outcomes for assessing clinical efficacy or effectiveness. There has been an explosion in the dietary supplement industry to use PROMIS questionnaires as incontrovertible proof toward unqualified structure function claims. Using PROMIS questionnaires as supportive subjective evidence in randomized, clinical trial designs with objective biomarkers and clinical assessments by medical professionals is the best way to evaluate dietary supplement products and make unqualified structure function claims. Structure function claims, based exclusively on PROMIS instruments, should be qualified in scope to the actual measurement used, which involves an assessment of the feelings and experiences of a participant's use of the test article. Claims that a dietary supplement product helps with occasional and joint recovery after physical exercise using PROMIS instruments would not be qualified enough or limited in scope to be substantiated. A more acceptable claim might be "helps consumer's experience of pain." If the clinical trial did not involve an objective assessment of the joint itself in range of motion and recovery by a trained health professional, one could not make a claim for joint recovery.

Below are the take home message talking points regarding use of PROMIS instruments in dietary supplement clinical trials:

- PROMIS instruments are gaining popularity in clinical trials in the areas of procedure interventions, behavioral interventions, device interventions, and dietary supplements. They are used to a lesser extent in drug therapeutic research and typically in the case of evaluating side effects of treatments experienced by study participants.

- PROMIS instruments do not involve objective biomarkers and clinical assessments by trained health professionals and therefore are unable to be used to support physiological outcomes of a study, recovery of function, return to function, etc.

- PROMIS instruments are better used as corroborative support in providing subjective feelings of participant experience as to the overall effects, and more importantly, side effects, of a test article when combined with consented, randomized clinical trials involving biomarkers and physiological assessment toward making substantiated structure function claims.

- PROMIS instruments should not be used alone to ascertain efficacy or clinical effectiveness of a dietary supplement or drug in a clinical trial.

- PROMIS instruments are not being properly applied to clinical research in the dietary supplement industry - blasting survey monkey questionnaires to ascertain subjective experiences and feelings from participants to support unqualified structure function claims fail to meet the burden of competent and reliable scientific evidence.

- Clinical trials involving only PROMIS instrument questionnaires are suitable to substantiate very limited-in-scope structure function claims about a participant's feelings in a certain aspect of their overall state of health, quality of life or behavior. They are not designed to provide substantiation toward any open-ended, unqualified structure function claim.

- Claims derived from PROMIS instrument questionnaires are more akin to claims made on cosmetic products, which discuss how the product makes one feel (e.g., perception of pain rather than eliminating pain and promoting recovery of the joint).

- Remote clinical trials must take extra precautions to ensure that study procedures are compliant with the standards of ethical human research, including proper informed consent procedures and sufficient medical oversight of the clinical trial. Sponsors of the clinical trial should ensure that they are not exposed to risk associated non-compliance.

- As with any research, the integrity of the data should be at the forefront of the research. Modern digital tools permit effective remote collection of data, but there must be effective procedures in place to ensure adequate compliance of participants with the study requirements. Compliance to the study procedures and taking the investigational product involves review of food records, study diaries, and counting test articles mailed back to the site overseeing the trial. Completely virtual trials that involve PROMIS instruments do not typically involve shipping unused product back to the site for verification.

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