Navigating the Challenges of Central Nervous System Disease Research

Planning for Success in CNS Clinical Development

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Nearly 1 in 6 People Suffer From a Neurologic Disorder Globally[1]

The prevalence of central nervous system (CNS) disease places a significant burden on health care systems and the patients and families living with these conditions. Increasingly, the morbidity and mortality caused by neurologic and psychiatric disorders are being recognized as a global public health challenge. Yet, despite meaningful advances in our understanding of the underlying pathophysiology of common CNS diseases, substantial unmet need remains, and development of novel treatment modalities has been slow.

Compounding this challenge is the ~85% failure rate of late-phase CNS trials. Potential sources of failure include lack of validated biomarkers, subjectivity of endpoints, disease and patient heterogeneity, high placebo response, and rater variability, in addition to country- and site-dependent regulations for controlled substances. To optimize the CNS trial strategy and increase the likelihood of signal detection and clinical and commercial success, sponsors must have a comprehensive understanding of the risks involved in every aspect of development and take necessary steps to mitigate them.

In this eBook, we offer insights into planning for success in CNS clinical development, with a focus on the dimensions of clinical trial strategy, patient experience, and evolving regulatory requirements.

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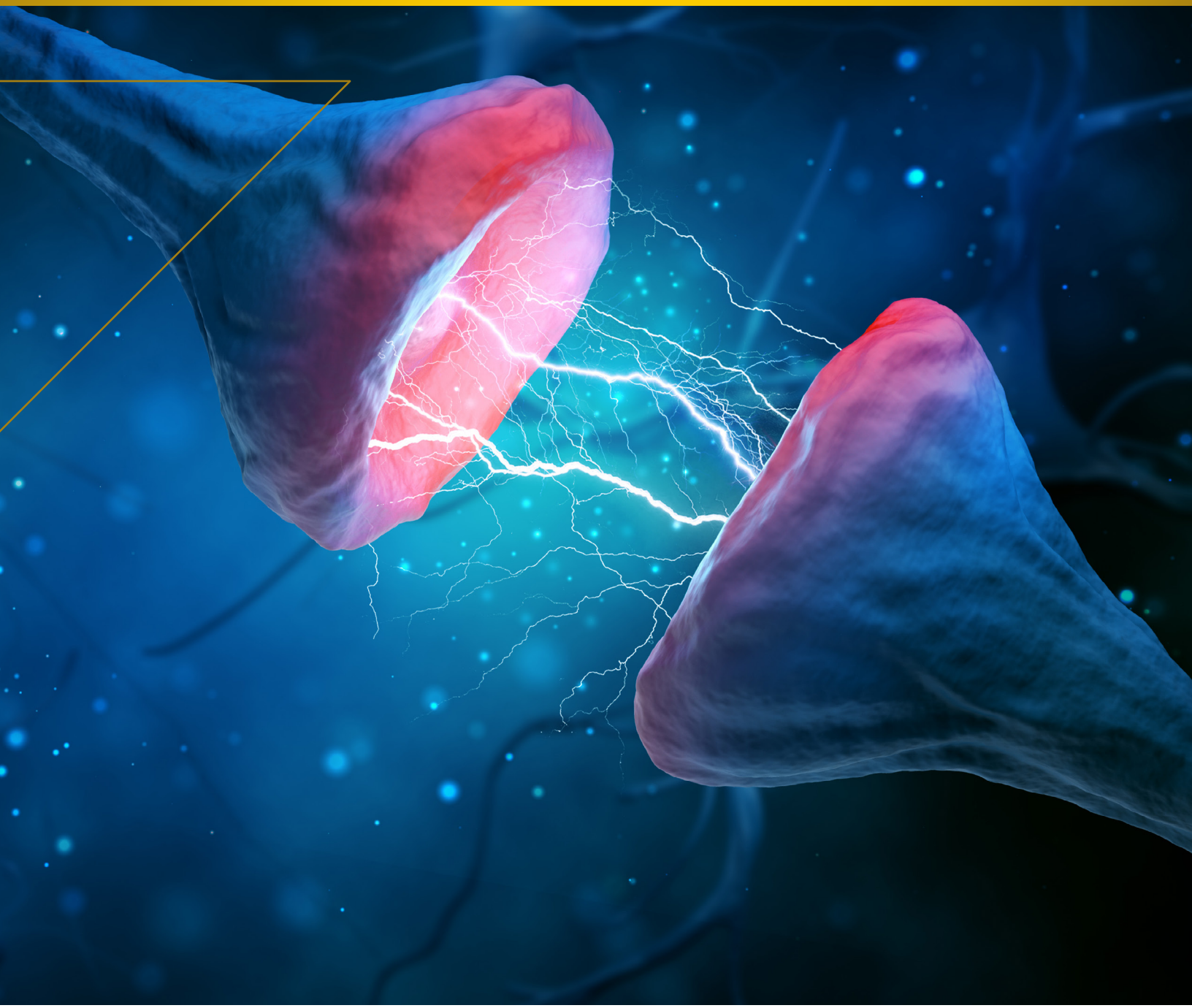


Chapter 1: Clinical Trial Strategies

Optimizing CNS Trial Strategy to Improve Signal Detection

The main source of trial failure across all indications is an inability to demonstrate efficacy.[2] Even potentially effective drugs can fail to demonstrate a treatment effect in clinical trials due to flaws in study design or issues with data quality.

In CNS studies, placebo response is often high, varying widely by indication and even geography, which confounds determinations of treatment effect. Moreover, signal detection can be impacted by several factors, including subjective endpoints, previous exposure to the drug class, heterogeneity in patient populations, disease presentation or progression, and rater variability.

Clinical Trial Strategies

Rater Training and Consistency

Rigorous study-wide training and centralized rater monitoring are key to minimizing subjectivity in CNS trials, in which less than 27% of studies successfully transition out of Phase II.[3] These trials rely heavily on subjective endpoints, such as psychiatric rating scales, to demonstrate efficacy and safety. However, variability in rater skill and training, differences in scales and diagnostic practices across geographies, diverse cultural and language needs, and lack of study-specific training present challenges to rater consistency.

Tips to improve rater consistency and minimize subjectivity

1. **Standardize study-wide rater training.** There is currently no accepted standard for selecting and training raters to administer scales, and raters may vary widely in their prior training and certification. This can lead to different assessment or interview methodologies across clinical trial participants, study visits, or scales. This challenge can be addressed with a structured rater training program that is defined and delivered at the outset of a study, with periodic retraining throughout the duration of the trial.

   As part of the training program, it may also be helpful to establish minimum rater qualifications, based on experience with the administration of the rating(s) required for the study. Rigorous training drives consistency study wide, leading to accurate, reproducible data. To avoid overburdening site personnel, all training should be efficient with allowances for experienced raters.

   Additional training courses may also be developed to help patients improve their ability to accurately and consistently self-report symptoms.

2. **Consider utilizing centralized rater programs.** Sponsors may also consider utilizing a cohort of experienced, calibrated raters to perform assessments via phone or videoconference. With remote assessments, raters are subject to fewer biases as they are not privy to details of the study or the patient's clinical history. This strategy can reduce site and patient burden, which may help to accelerate study startup and enrollment.

   Centralized rater programs also increase clinical trial access for sites and patients, expand eligibility pools, and enhance clinical trial diversity and equity. To ensure proper training, documentation, and data quality, it is important to define the manner in which the rating scale will be administered.

3. **Establish centralized rater monitoring.** Rater surveillance programs can help to minimize subjectivity by providing oversight of key assessments. Monitors can perform independent or confirmatory reviews of assessments to ensure that scoring and administration conventions were followed and appropriate interview techniques were used.

   Visualizing clinical assessment data across an entire study helps monitors and sponsors detect patterns or potential issues in rater consistency and accuracy. For instance, if a site is generating unusually high or low values, the issue can be investigated and additional training can be provided. Centralized rater monitoring also includes scheduled assessments of rater consistency and reliability to help mitigate rater drift, which can adversely impact data quality, particularly in prolonged studies. If drift is detected, immediate refresher training can be initiated.

Key takeaways

Embracing the development and implementation of rigorous study-wide training for all raters helps to enhance consistency and minimize subjectivity. For studies in which remote assessments are feasible, the use of centralized raters can further reduce bias. This monitoring approach helps to detect, mitigate, and remediate inter- or intrarater drift during the study, ensuring that rating assessments can be relied on as primary or secondary endpoints. For both rater approaches, centralized and decentralized, it is crucial to address the methodology and associated documentation during the startup phase, defining who, when, where, and how the scale is to be administrated for each visit.

Clinical Trial Strategies

Centralized vs Decentralized Raters

CNS disorders can manifest differently among individuals, making it challenging to consistently assess treatment efficacy. This is exacerbated by the subjective nature of patient-reported outcomes, which may be affected by mood, personality, or other cognitive factors. These factors underscore the importance of minimizing variability wherever possible. Following standardized protocols can allow for more accurate comparisons between treatment groups, reducing the potential for bias.

In clinical trials, there are 2 approaches to rating, which differ in location and number of raters:

- **Centralized rating** involves a single group of raters, often at a central location, that assess the symptoms and outcomes of study participants using standardized assessment tools. This approach aims to minimize the potential for rater bias and variability.
- **Decentralized rating** involves raters at multiple sites or locations. This approach aims to increase the efficiency of data collection by distributing the workload across multiple raters and may be more practical for studies that involve large geographic areas or diverse populations.

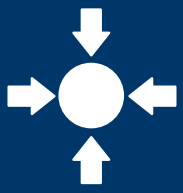
Each rating approach has advantages and disadvantages, and the choice of which approach to use depends on the specific needs of the clinical trial (see Figure 1). For example, centralized rating may be preferred for studies that require complex assessments or a high level of standardization and consistency. Decentralized rating may be preferable when flexibility and efficiency of data collection are required.

Tips for implementing centralized rating

Careful planning, training, and monitoring are important when implementing a centralized rating approach. Additionally, multistakeholder collaboration helps to define optimal workflows and supporting processes. The outcome measures to be assessed first are defined in the study protocol. Then, successful implementation involves these important steps:

1. **Identify a group of experienced, qualified raters** with expertise in the outcome measure(s) being assessed and experience in conducting centralized ratings
2. **Determine technology needs** that are necessary to support centralized rating, whether using electronic patient-reported outcomes (ePROs) or electronic clinical outcomes assessments (eCOAs), and select qualified vendors
3. **Develop and implement a standardized rater training program** that covers the rating scale(s) to be used, including practical training to ensure that all raters apply the rating scale in a consistent manner
4. **Conduct a reliability study** to assess interrater reliability. This involves multiple raters independently rating a set of standardized cases to evaluate consistency among their individual ratings
5. **Monitor rating quality throughout the study** with regular review of a sample of the ratings to ensure there is no rating drift
6. **Provide ongoing training, support, and supervision** for the duration of the study

Figure 1. **Advantages and Disadvantages of Rating Approaches**

+ Advantages		– Disadvantages
+ Increased patient access and convenience, which may help with recruitment and retention + Bigger pool of eligible sites, since sites no longer need to have their own expert clinical raters + Centralized reporting, which allows rapid identification and remediation of noncompliant visits + Well-trained, independent raters may be more objective in determining eligibility and treatment effectiveness + Rating standardization due to centralized training and calibration, which leads to higher levels of intra- and interrater reliability + Ability to study patient in real-world settings, rather than the clinical trial environment	**Centralized Rating** 	– Fewer face-to-face interactions with study staff – Need for good connectivity and technology capability for both sites and study participants – Cost, depending on the study protocol and design
+ Assessment by a provider who knows the patient, which may be more comfortable for the patient + Provision of on-site care, which clinical trial participants may expect or prefer	**Decentralized Rating** 	– Difficulty in achieving standardization at a study-wide level – Cost and time involved in hiring, training, and maintaining expert raters at each study site

Considerations for Determining the Appropriate Rating Approach

Indication under investigation

Disease complexity, symptomatology, or rate of progression can influence the rating process. For certain conditions in which specialized training and experience are required to evaluate symptom severity accurately, centralized rating may be more appropriate. This is also true for studies in which the ratings are primary or secondary endpoints.

Study design

The frequency of evaluations and the feasibility of performing those evaluations remotely also affect the choice of rating approach. For studies that require frequent or in-person assessments, decentralized rating may be the most cost-effective option.

Investigator experience

Seasoned investigators may have a better understanding of the disease under investigation and the potential side effects or complications of the treatment being tested, making them better equipped to identify and measure the outcomes of interest. They may also be more familiar with the tools and methods used to assess these outcomes, which helps ensure that the data collected are reliable and accurate with either rating approach.

Site experience

Certain sites have greater skill working with the patient population of interest. They may also have more resources or an infrastructure in place to ensure the quality and accuracy of data collected with decentralized rating. Sites without expert raters may benefit from a centralized approach to accelerate study startup since hiring, training, testing, and overseeing local raters may be more costly and time consuming.

Rating scale(s) used

These scales vary in complexity and level of validation or availability of expert guidelines or published literature to support interpretation. Country involvement, availability of certified translations, and any licensing requirements must also be considered. One study evaluating different versions of the Hamilton Rating Scale for Depression (HAM-D) found that these versions varied in their clinimetric properties, concluding that the most appropriate version for a clinical trial would depend on rater experience, study design and objectives, and clinical characteristics of the population being evaluated.[4]

- For rating scales that require visual assessment, centralized rating has the advantage of reducing variability in ratings since all raters are trained and supervised in a standardized fashion.
- For rating scales that are complex and require significant and ongoing training and oversight to ensure compliance and consistency, centralized rating may be more appropriate.

Likelihood of placebo response, response bias, and rater bias

The characteristics of both patients and raters can impact rating measurements.

- With patients, placebo response occurs when the positive expectation of improvement impacts self-reported outcomes. In clinical trials of antidepressant medications, placebo response is substantial.[5] Response bias is introduced when patients answer rating questionnaire items with the response they perceive to be most desirable to the rater or study staff.
- With raters, bias can be introduced when the rater's underlying beliefs regarding the treatment under investigation influence their rating. When the level of placebo response, response bias, or rater bias is expected to be high, utilizing centralized raters to perform both the screening and outcome measures of a study may minimize bias and maximize consistency.

For some studies, a hybrid approach that combines both centralized and decentralized rating may be appropriate. For example, a trial could use local raters to screen for eligibility and central raters to assess for efficacy, provided that all raters receive the same training and testing. In CNS conditions such as Alzheimer's disease, for which telemedicine examinations correlate well with in-person evaluations, using the patient's own physician—under the direction of two central neurologists—to perform rating assessments maintains consistency and may help to accelerate enrollment.[6]

Key takeaways

Rating plays a critical role in CNS trials, providing a standardized and objective method for evaluating the efficacy and safety of investigational treatments. There is no one-size-fits-all approach to rating in CNS trials. Determining whether to implement a centralized, decentralized, or hybrid approach requires careful consideration of the study objectives and outcome measures, with a focus on optimizing the reliability, validity, and accuracy of results.

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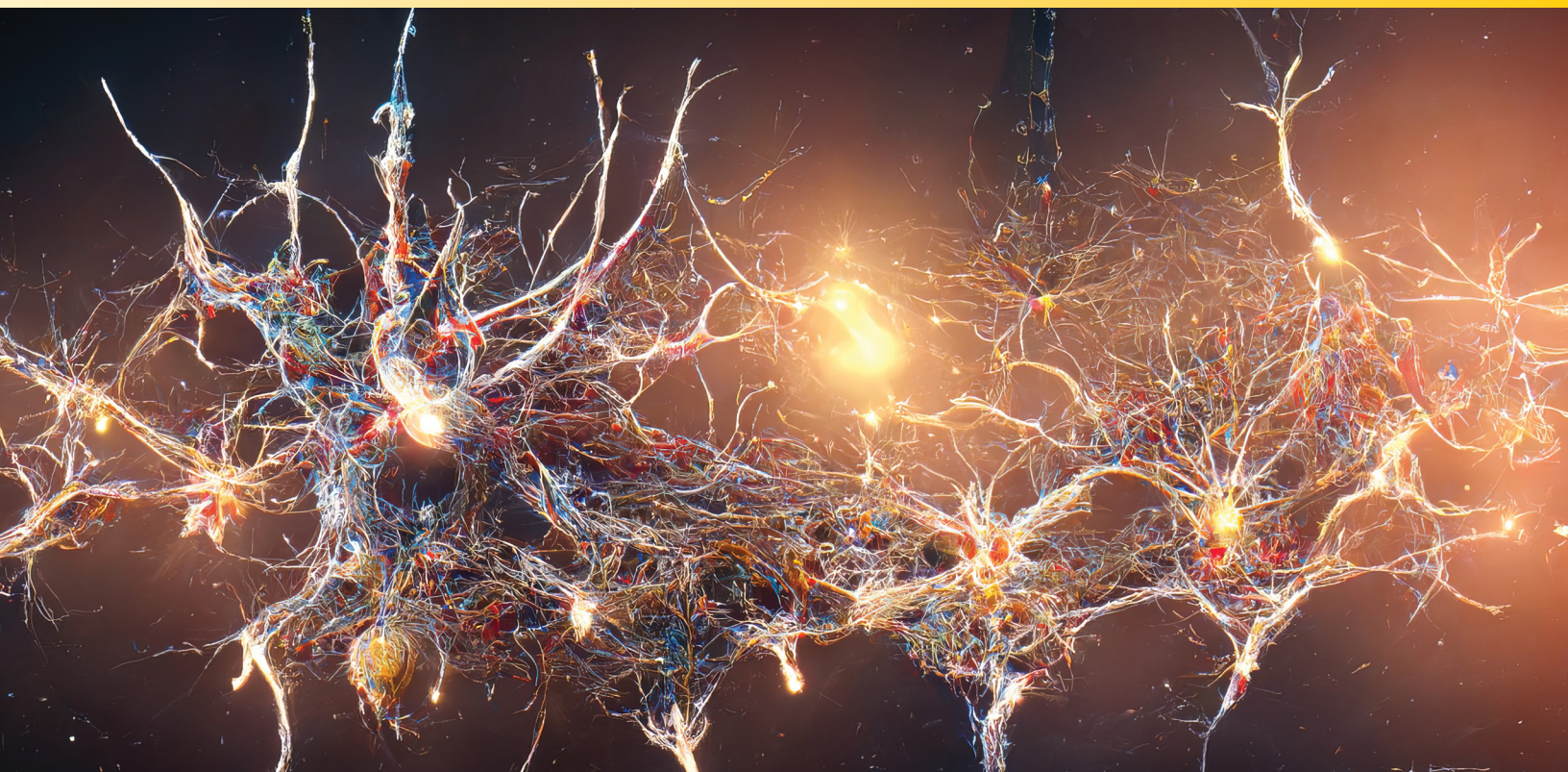
No One-Size-Fits-All Approach for Rating

Deciding whether to use centralized or decentralized rating involves careful consideration of every facet of a study, from the disease and population of interest to the type and frequency of rating assessments.



Chapter 2: Patient Experience

Enhancing the Patient Experience in CNS Clinical Trials
Advancements in technology and increased emphasis on patient-centered clinical trials are accelerants of health care's digital transformation.

To keep pace, sponsors are tasked with integrating data collection capabilities into their studies, while balancing the dual priorities of optimizing data quality and enhancing the patient experience. Especially in CNS clinical trials, in which endpoints are often subjective or self-reported, a deep understanding of—and focus on—the patient is paramount.

Patient Experience

Incorporating Decentralized Clinical Trial Strategies

Decentralized clinical trial (DCT) strategies emerged quickly during the COVID-19 pandemic. However, as pharmaceutical and biotech companies explore this new frontier more deliberately, interest has cooled somewhat as they assess the best path forward.

Many sponsors are cautiously optimistic about DCTs but remain aware of their limitations.

Promising DCT strategies for CNS drug development

Several DCT strategies hold promise for CNS drug development, offering potential benefits such as increased patient recruitment, improved adherence, and enhanced data collection.

- **In-home nursing visits.** These can be highly beneficial for patients with conditions such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis (ALS). Bringing skilled care into the patient's home reduces the stress and physical burden of travel, particularly for those with functional limitations or advanced disease stages. In-home visits can also provide unique insights into a patient's everyday functioning, potentially improving the sensitivity of assessments.
- **Direct-to-patient drug delivery.** This brings investigational drugs directly to patients' homes, which can be crucial for those who have mobility issues or live far from clinical sites. This strategy can be beneficial for patients with CNS diseases such as ALS, who may have severe physical disabilities.
- **Mobile health technologies.** Products such as wearable devices provide real-time data on patient health metrics, offering invaluable insight into treatment efficacy and patient adherence. For conditions like Parkinson's disease, with which symptom severity can fluctuate throughout the day, wearables can help capture these variations in a way traditional clinical visits may miss.
- **Electronic patient-reported outcomes (ePROs).** Commonly used in traditional CNS trials, **ePRO tools are a vital component of decentralized clinical trials**. They allow patients to report symptoms and side effects in real time, providing a more comprehensive and accurate picture of the patient's experience. For CNS trials, ePROs can enhance our understanding of disease progression and the impact of interventions on quality of life.
- **Gamification,** a powerful strategy to keep patients engaged, gamified elements can transform mundane or repetitive tasks into enjoyable activities, thereby improving patient participation. In CNS trials, especially for conditions such as attention-deficit/hyperactivity disorder (ADHD) or cognitive impairment disorders, games can serve a dual purpose of collecting data while improving cognitive functions and maintaining patient engagement.

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Fit-for-Purpose Trial Design

By **tailoring trial design to the unique needs and challenges** of different CNS conditions, sponsors can ensure that innovation enhances, rather than compromises, the quality of clinical research.

Challenges of DCTs in CNS drug development

Not all DCT strategies are equally effective across all conditions. Some may require in-person assessment or interventions that are difficult to conduct remotely.

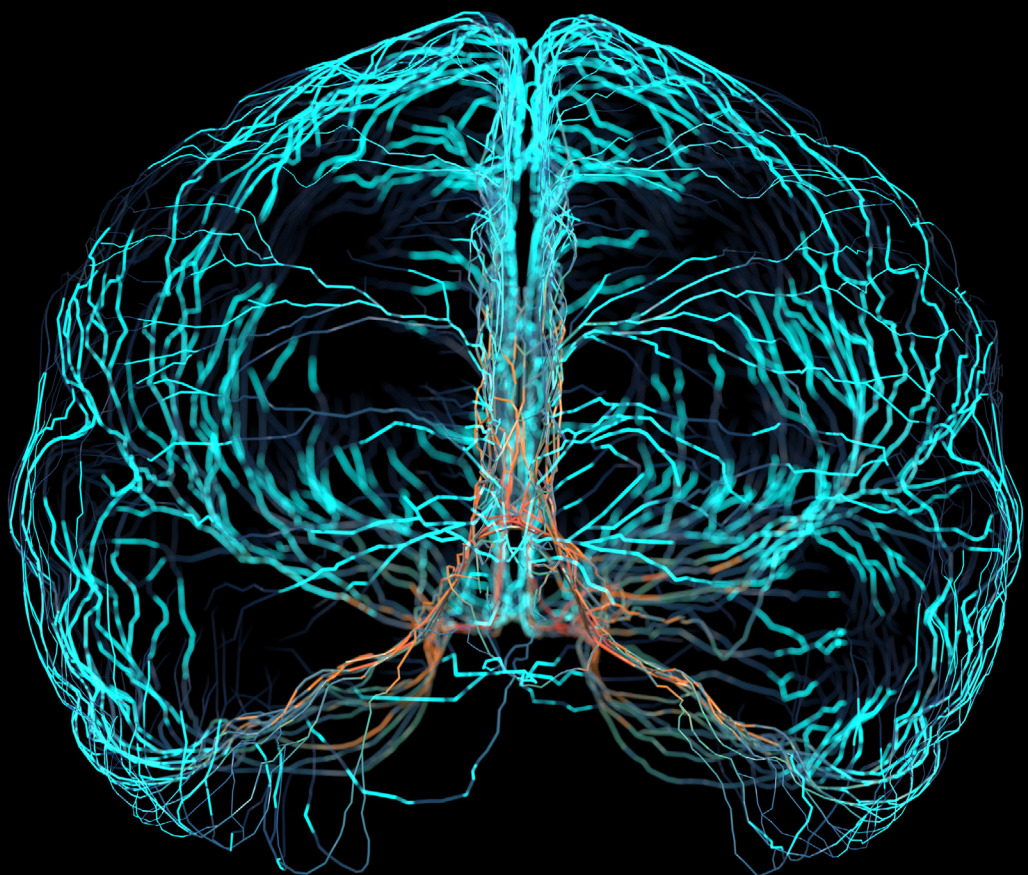
For instance, Alzheimer's disease and other dementias can be challenging to monitor remotely. While telemedicine and digital health coaching may provide some insight, nuanced changes in cognitive function and motor deficits can be difficult to assess without face-to-face interaction. Similarly, for conditions such as epilepsy, in which seizures can be nonconvulsive and hard to detect remotely, traditional in-person evaluations may still be necessary to monitor medication side effects and overall health status.

Implementation of a hybrid approach

Given the complexities and variability of CNS programs, many sponsors have adopted a hybrid approach. This combines traditional in-person trials with decentralized strategies, offering a flexible approach that caters to the needs of different patient groups and disease states. Hybrid models enable sponsors to leverage the advantages of DCT techniques to support broader patient recruitment and improved convenience, while preserving essential aspects of traditional in-person trials.

Key takeaways

While DCTs present an exciting opportunity for improving the efficiency and patient-centricity of CNS drug development, thoughtful hybrid approaches seem most promising. The future of CNS drug development will be about finding the right balance to deliver the best outcomes for patients, investigators, and sponsors.



Patient Experience

Electronic Patient-Reported Outcomes

Using ePRO technology can help address some of the key challenges of CNS research.

ePRO solutions are designed to optimize the objectivity of inherently subjective data by allowing for more frequent and timely data collection. With the right design and implementation, use of ePRO technology can help to reduce the influence of placebo response, improve patient engagement and adherence, and identify true treatment effects.

Using ePRO technology offers several potential advantages in CNS trials:

- Automated input validation, which helps ensure that entries are valid and complete. Studies have shown that ePROs are typically associated with fewer missing data[7]
- Greater data integrity due to electronic time stamps, which may encourage more timely entries
- Enhanced sense of privacy that comes with self-recording symptoms and other sensitive feedback outside of the clinical trial setting
- Reduced number of secondary data entry errors associated with transcription of paper patient-reported outcomes (PROs) into the study database
- Higher compliance compared to paper PROs due to ease of use and ability to send alerts when assessments are scheduled or missed
- Improved recruitment and retention due to decreased patient burden by reducing the number of site visits and assessments required, which helps limit travel and may make the study available to a wider, more diverse patient pool
- Decreased site burden because ePRO technology allows for remote data collection, which can automate the process of collecting and storing PRO data and reduce the need for in-person visits
- Capability to send automated reminders and instructions about study-related tasks
- Enhanced safety, with ePROs that have real-time data monitoring features that allow messages to be sent to patients if their responses meet predetermined thresholds

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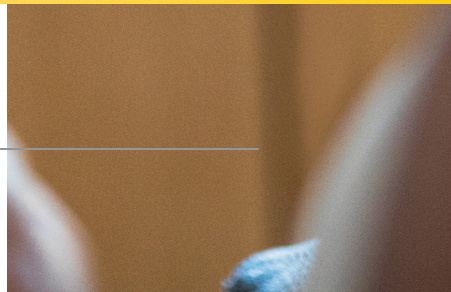
Thoughtful Implementation Is Key

Although each study and its ePRO requirements are unique, there are best practices for implementing solutions that minimize patient and site burden while maximizing data value.



Best practices for designing, developing, and deploying ePROs

1. **Define study objectives and identify potential patient-reported outcome measures (PROMs).** Developing clear study goals helps clarify what PROM data need to be collected and how these data will be used to evaluate treatment effectiveness. In November 2022 the National Quality Forum issued **technical guidance on how to select high-quality PROMs for use as performance measures** and how to develop digital patient-reported outcome performance measures (PRO-PMs, or ePROs). This guidance defines 12 attributes of PROMs that are appropriate for use in digital PRO-PMs and outlines a 4-stage roadmap for developing a digital PRO-PM. Beyond reliability and validity, key attributes of an appropriate PROM include[8]:

    - Meaningfulness and relevance from the patient and/or caregiver perspective
    - Interpretable scores and defined and actionable cut points or targets
    - Low patient burden in terms of the length of the assessment and the time or effort needed to complete it
    - Fit with the standard of care and related workflow to minimize site burden
    - Cultural appropriateness for each setting of use

    Creating and seeking feedback from a stakeholder advisory group that includes patients, caregivers, patient advocacy groups, clinicians, and payers ensure that the PROM reflects the perspectives of all those who will be affected by the measure or its completion and collection process.

2. **Design a fit-for-purpose ePRO.** When designing an ePRO, it is essential to consider the overall complexity of the study and the associated patient and site burden. The usability, design, timing of questions, and alarms are all integral to successful implementation and execution of ePRO. Engaging subject matter experts (SMEs) from the ePRO vendor to work on the design and build is especially important in complex studies. An important consideration for ePRO design is whether to provide devices or to use a bring-your-own-device (BYOD) model. This decision may be informed, in part, by the nature of the assessment. Participant preference should also be factored into this decision.

    - *Keep in mind that some measures have specific device requirements that may not be suitable for a BYOD approach.*

    While some participants may prefer the convenience and privacy of using their own device, others may be hesitant about downloading an app or paying for cellular data use. In addition to regulatory compliance and device security, accessibility may also be an issue for the BYOD model if the target population has low rates of smartphone use.

    - *There exists significant fragmentation among mobile devices regarding versions and operating systems.*

    Another important consideration is how the ePRO system will integrate with other study technologies. Bringing together all technology vendors prior to building the ePRO system enables better coordination of services to optimize efficiency and the sponsor, site, and patient experience.

    - *For trials that last a number of years, devices may have to be decommissioned and upgraded.*

3. **Test the ePRO system.** The ePRO system should be tested for reliability, validity, and user acceptance in the settings and with the populations where it will be used. User acceptance testing (UAT) should include a 24-hour test to ensure that diary reminders and alarms trigger as expected. Working with an ePRO vendor that offers robust site and patient support services is critical for ensuring adoption and acceptance.

4. **Develop ePRO training materials.** Creating and implementing online training programs that educate patients, caregivers, and sites on the proper use of the software and devices used to complete ePROs can help to maximize adherence and data quality and minimize placebo response rate. The training should include information on the purpose and use of the ePRO system, the importance of accurate and complete data, and detailed guidance on entering data. It may be helpful for this training to include instructions on how to confirm that internet connectivity is strong and stable enough to send and receive ePRO data and whom to call for troubleshooting assistance.

5. **Create a backup plan.** Having a contingency plan in case there are issues with ePRO data collection or submission can help minimize the risk of missing data. This contingency may be a paper PRO that has been validated to be equivalent to the ePRO.

Key takeaways

With proper planning and intelligent deployment, ePRO technology can help address some of the key challenges of CNS trials. To minimize site burden and ensure compliance with regulations for electronic recordkeeping, sponsors must ensure that all study-related technology solutions work together as seamlessly as possible. Thus early coordination among clinical research organization (CRO) partners and vendors prior to ePRO system development is critical.

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Intelligent Integration of ePRO Technology

At Precision for Medicine, we have deep expertise in managing CNS trials that leverage ePROs and extensive experience in working with ePRO vendors to integrate their systems with other study technologies. To learn more about our more than 25 years of experience, click here.

Chapter 3: Regulatory Considerations

Unlocking the Potential of Controlled Substances

For many CNS disorders, treatment options are limited, and those that are available typically offer symptomatic relief rather than disease modification. In recent years, controlled substances have emerged as promising treatment options for a range of neurologic conditions.

These substances often have unique mechanisms of action compared to traditional pharmaceuticals and can exert significant effects on neurotransmitter systems in the brain. Compelling preclinical evidence, coupled with advances in neuroimaging technology that facilitate study of the effects of controlled substances on the brain, has led to a sharp increase in the number of CNS clinical trials investigating the therapeutic application of controlled substances. However, because of the associated regulatory and logistical hurdles, these trials require careful planning and meticulous execution.

Regulatory Considerations

The Rise, Risk, and Regulation of Controlled Substance Research

The number of CNS clinical trials involving controlled substances has been consistently increasing, particularly in the past 2 years (Figure 2). This upward trend demonstrates the heightened interest in CNS research and the growing acceptance of studying controlled substances in prominent markets.

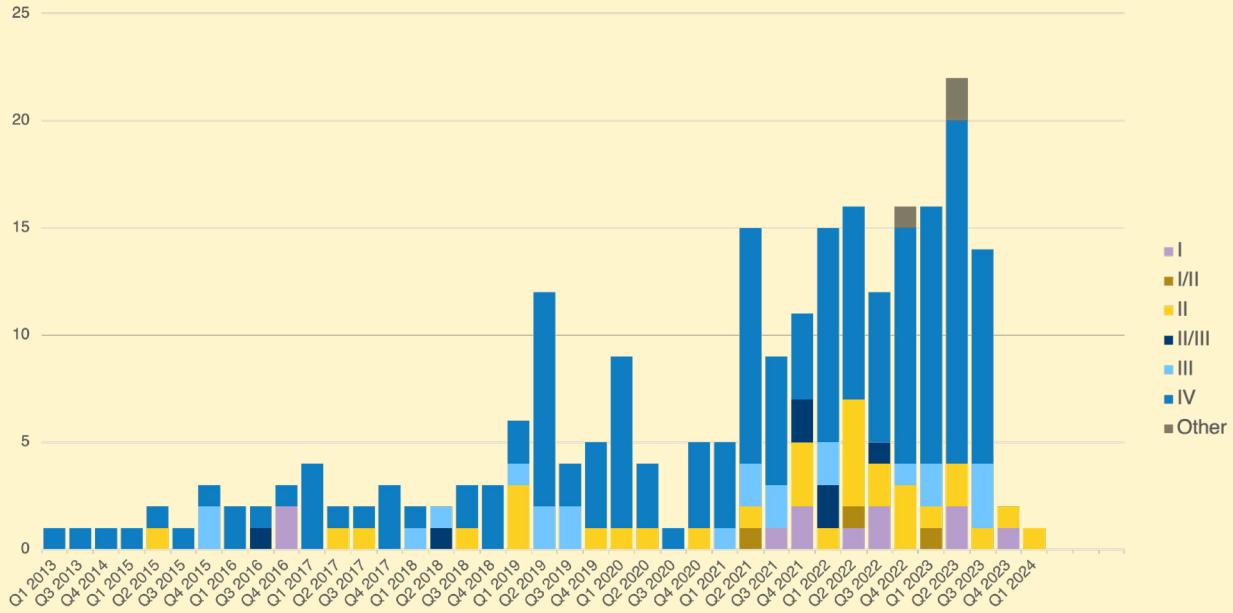

Figure 2. **EU Controlled Substance CNS Trials From Q1 2013-Q1 2024**

Indications

The ability of these substances to interact with receptors in the brain and alter consciousness demonstrates the potential for therapeutic benefits across a range of psychiatric, neurologic, and pain disorders (Figure 3).

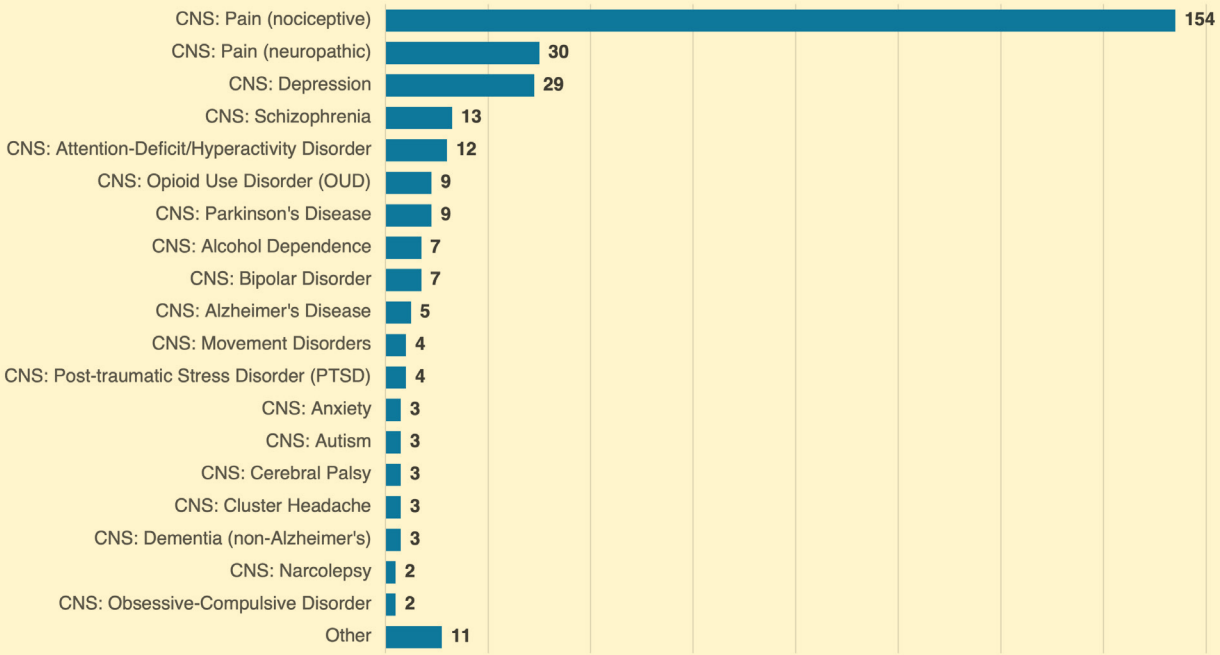

Figure 3. **CNS Trials in the EU Involving Controlled Substances, by Indication[9]**

Critical startup phase for controlled substance trials

Due to the added oversight and restrictions around controlled substances, the startup phase requires extra attention compared to standard clinical trials. Sponsors must proactively identify and mitigate risks early to prevent delays. Key startup tasks include:

- Thoroughly assessing regulations and import/export laws when selecting trial countries as this can impact study timelines
- Developing distribution procedures adhering to each country's security and documentation rules for controlled substances
- Having protocols reviewed well in advance by the appropriate regulatory authorities and ethics committees
- Evaluating if qualified pharmacies are available to securely manage drug supply and reconciliation
- Verifying sites have proper facilities and resources to store and administer controlled drugs
- Training staff on proper handling, administration, inventory, and reconciliation procedures
- Implementing robust supervision and auditing practices to quickly identify any deviations or other issues

Mitigation of risk during CNS controlled substance trials

Preventing controlled drug diversion or misconduct is critical from a liability standpoint. Proper vigilance and protocols are the pillars of risk management in studies with scheduled drugs. Recommended risk mitigation strategies include:

- Background screening for staff handling the drugs
- Restricted access to controlled substances
- Detailed inventory logs and reconciliation processes
- Random audits of drug storage locations
- Secure transfer containers and tamper-evident seals
- Video surveillance and alarms where substances are kept
- Prompt drug destruction after trials

Regulatory landscape of controlled substance research

Regulations for the study of these controlled substances encompass a wide range, including the selection of trial countries, import/export laws, distribution procedures, and adherence to security and documentation rules. Each country has its own set of regulations and import/export laws that must be thoroughly assessed when selecting trial countries, as they can significantly impact study timelines.

This underscores the importance of partnering a CRO with the right regulatory expertise.

Regulatory Considerations

Navigating DEA Controlled Substance Regulations

Due to the specific regulatory and logistical challenges related to adhering to the controlled substance regulations imposed by the US Drug Enforcement Administration (DEA), sponsors may have concerns about conducting a clinical study involving controlled substances. For those interested in venturing into this area, it is important to consider the following practical points when planning your program:

1. **Analyze regulatory and governmental guidance.** Given the addictive and hazardous nature of controlled substances, as well as their high street value, security against theft or diversion during clinical trials is a key concern and responsibility for sponsors. For US-based studies, the DEA regulates transportation and storage of **schedule I-V controlled substances (21 CFR 1308)** outlined in the **1970 Controlled Substances Act (CSA)**. Schedule I lists the most tightly controlled drugs and includes drugs with high abuse potential that currently have no accepted medical use.

   In the past, guidance for recordkeeping and handling of these drugs was limited to a few paragraphs in the Code of Federal Regulations (CFR), such as 21 CFR 312.62 and CFR 312.69. However, the **June 2022 DEA Researcher's Manual revision** adds much-needed detail and clarity regarding controlled substance handling throughout the research journey, from receipt of clinical trial materials through dispensing or destruction. Combining a deep understanding of the regulatory expectations with thoughtful implementation is the best way for research projects to weather regulatory scrutiny.

2. **Register with DEA well in advance.** Every US principal investigator (PI) intending to conduct a study on any scheduled substance must **register or renew registration with DEA** via Form 225. The PI must also obtain a corresponding state license and/or controlled substance registration. Variations in regulations from state to state or country to country increase the complexity of study management. Separate registrations must be obtained for each location where controlled substances will be stored or given.

   A wait time of 3 to 6 months is possible for issuance of a certificate. Generally, registration must be renewed annually, but the first renewal date may occur earlier than that, so be alert and keep every address on file at DEA current. Beyond registration, a schedule I researcher must also submit a curriculum vitae and research protocol for evaluation and obtain approval from their own institution(s). It is recommended that schedule I researchers comply with all applicable state laws and regulations before applying for DEA certification.

3. **Navigate logistics correctly.** For use and distribution within clinical studies in the US, schedule I and II drugs must be ordered using DEA Form 222. These numbered, nontransferable forms are issued uniquely to registrants, with unalterable, identifying information. The purchaser must complete the form, retain a copy, and submit the original with the order. Later, once the order has been filled, the purchaser must document on their copy of the order form when and how much of the order was received. The supplier retains the original Form 222 with their records. Alternatively, sponsors may use the Controlled Substance Ordering System (CSOS) to submit orders electronically.

Disposal of unused controlled substances

If disposal is performed via a reverse distributor, special rules apply. For schedule I and II substances, reverse distributors must issue a DEA Form 222 to the researcher. Once the items have been destroyed, the reverse distributor must submit a DEA Form 41 to DEA.

4. **Understand site requirements for studies involving DEA-regulated controlled substance studies.** Sites for controlled substance clinical trials must have DEA antitheft and **diversion prevention** plans in place and approved physical security and drug storage facilities **(21 CFR 1301.71, 21 CFR 1301.72)**, such as alarmed, substantially constructed locked cabinets or safes **(21 CFR 312.69)**. Sites must also have trained personnel and systems that ensure consistent performance of correct recordkeeping and inventory activities. The DEA field office will visit sites to verify that they meet security requirements. Local inspections (such as by the Research Advisory Panel of California, RAPC) may take place as well.

   To provide accountability and discourage diversion, researchers must maintain easily accessed, complete, accurate, and current records for every schedule I-V controlled substance that comes into their site and retain them for 2 years. Similarly, inventories must remain available at certified sites for at least 2 years.

   Evaluation of site feasibility must also consider any applicable country-specific regulations. Consultation with partners who not only know these regulations but also maintain lists of investigators and sites with DEA-related experience can prevent delays in certification and errors in study execution later.

5. **Tackle recruitment and retention challenges for CNS controlled substance trials.** Recruiting patients with mental health disorders may be difficult. They might not wish to receive the placebo or may be apprehensive regarding controlled substances. A partner with experience in recruiting and retaining subjects in CNS clinical trials utilizing controlled substances should have strategies to help study participants see things differently and decrease their reluctance to enroll in a controlled substance study.

Key takeaways

CNS trials involving controlled substances face challenging regulatory requirements for study startup, supply chain logistics, site operations, and patient recruitment. Sponsors must plan carefully to ensure consistent compliance for their controlled substance studies. Organization and experience go hand in hand to make these trials work.

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Leverage External Expertise

Partnering with the right CRO is essential to navigating the regulatory complexities of controlled substance studies and choreographing the logistics of safe, compliant intellectual property (IP) management.

Regulatory Considerations

Studies of Controlled Substances in the EU

Running these trials successfully in the European Union (EU) requires a thorough understanding of the laws and regulations surrounding this category of drugs across member states. In this section, we outline key considerations for sponsors seeking to conduct controlled substance clinical trials in the EU.

The EU is an attractive destination for these studies due to the availability of diverse patients, expertise, and infrastructure that can support the investigation of the safety and efficacy of these substances for therapeutic application.

Overview of EU regulations for controlled substances

Each European country categorizes controlled substances differently based on international drug conventions. The level of control depends on the substance's potential for harm or abuse: high-risk drugs face stricter regulations than lower-risk ones. While the EU Clinical Trials Regulation (EU-CTR) harmonizes processes for clinical trials across Europe, controlled substance protocols still require individual country approvals. Compared to other investigational drugs, these compounds require extra steps for handling, administration, and oversight. These measures aim to prevent diversion and ensure proper use, but they also create logistical complexities versus standard clinical trials. Consequently, sponsors must budget more time and resources when working with controlled substances.

Regulation differences across European countries

Under the EU-CTR, some of the previous differences in definitions and procedures for controlled substances have given way to more uniformity across Europe (Figure 4). For example, rules for importing, storing, and transporting these drugs are now standardized. However, some country-specific nuances remain regarding aspects such as license applications, dose preparation, documentation, and destruction requirements.

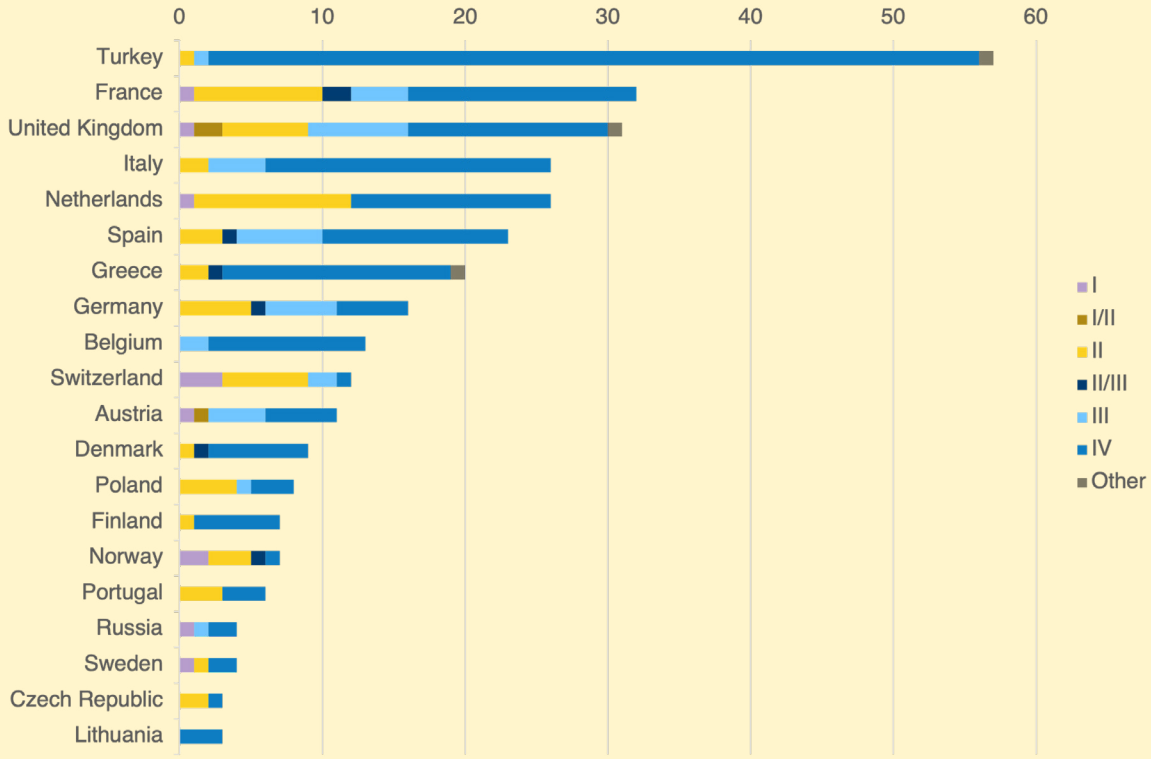

Figure 4. **Top 20 EU Countries Running Controlled Substance Clinical Trials, by Number and Trial Phase[9]**

While the changes resulting from the EU-CTR have helped to streamline certain requirements, sponsors still need to navigate individual country variations and nuances. When planning a study, sponsors must verify the current laws in each target country to ensure understanding of—and compliance with—local legislation.

Looking ahead

As the field of CNS research using controlled substances expands, the EU-CTR will continue unifying processes, although some country-specific nuances are likely to remain. By staying current on evolving regulations and partnering with an experienced CRO, sponsors can navigate these requirements confidently.

Wired for CNS

Map Country-Specific Nuances During Feasibility

It is critical to map and document the controlled substance nuances within each country and investigative site. Incorporating into your feasibility project appropriate questions about controlled substances as part of study startup activities will help create a solid foundation for efficient site selection and onboarding.

Conclusion

Successfully developing CNS treatments requires deep understanding and specialized expertise. Precision for Medicine is wired for CNS, combining the right expertise, capabilities, and technologies to alleviate pain points and free sponsors to focus on overseeing and selecting solutions rather than creating them.

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About the Authors

Robert Bauer

Executive Director, Operational Strategy—Feasibility and Ops Strategy

Robert brings more than 20 years of clinical trial operations experience from both the sponsor and CRO perspectives. He has led teams in the conduct of trials from Phase I through IV and has experience across a wide variety of trial designs. His experience spans many therapeutic areas, including rare diseases, oncology, depression, schizophrenia, and substance use disorders.

Saoussen Brun

Senior Director, Project Management

Saoussen brings nearly 20 years of Clinical and Project Management experience to the Precision team. Her expertise covers a wide variety of therapeutic areas, with strong roots in oncology and neurology indications. She leads and motivates high-performing teams under tough deadlines to meet both project goals and company targets.

Tracey Owens

Director, Project Management

Tracey has almost 30 years of experience in managing Phase I through IV clinical trials. She is highly experienced in providing directional oversight on rare disease, CNS, psychiatric, and oncology clinical trials. Her experience notably includes ALS, bipolar disorder, epilepsy, major depressive disorder, schizophrenia, idiopathic hypersomnia, chronic inflammatory demyelinating polyneuropathy (CIDP), traumatic brain injury, multiple myeloma, and dementia (including Alzheimer's and Parkinson's disease).

Vincent Shortino

Principal Clinical Trial Manager—Clinical Operations

Vincent brings more than 20 years of experience to Precision. His experience spans all major therapeutic areas with a heavy emphasis on cardiovascular and rare indications across Phases I through IV. His solid perspectives are inclusive of sites, pharma, and CROs from his previous roles of Study Coordinator, Site Director, Clinical Research Associate, and Clinical Trial Manager.

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