CLINICAL MONITORING CHALLENGES IN HUMAN ABUSE LIABILITY STUDIES

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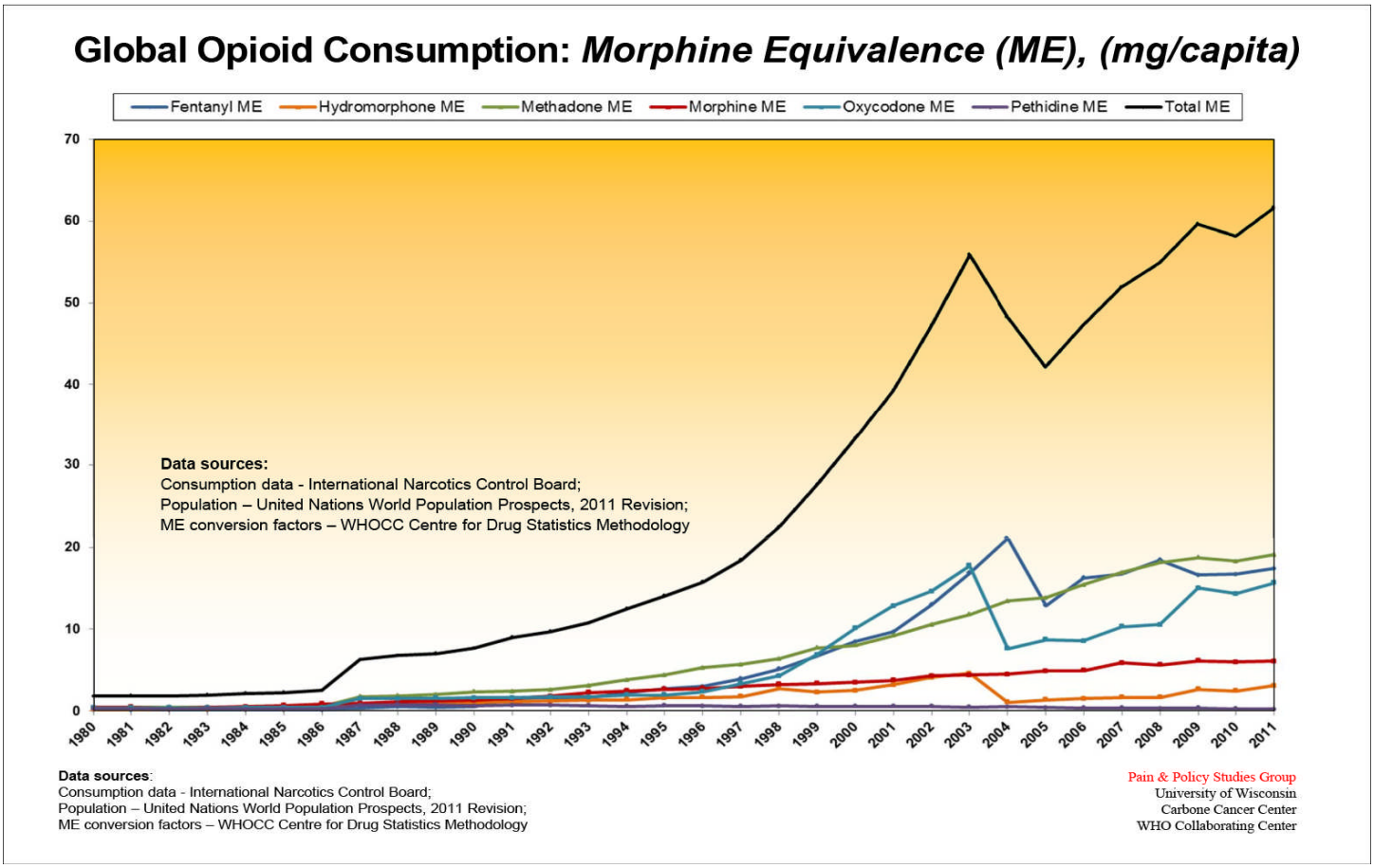
Clinical trials conducted to assess the potential for a drug to be abused stand out as specialized, complex studies in the already specialized and complex field of clinical development. And they are becoming more necessary and commonplace with the volume of compounds targeting the central nervous system.

The global use of opioids (as measured in morphine equivalence) has grown exponentially over the past two decades, as reported by the International Narcotics Control Board (INCB) (See Figure 1). Interestingly, the greatest use is in the U.S., which represents 5.5 percent of the world population and accounts for 55.9 percent of morphine consumption.[1] *According to a U.S. Drug Enforcement Administration (DEA) report, "Prescription drug abuse continues to be the nation's fastest growing drug problem,"*[2] *with more than 4.5 million Americans abusing pain relievers. The National Institute on Drug Abuse reported that approximately 26 million Americans (8 percent of the population) said that they'd used a prescription drug for nonmedical reasons in the prior year. The drugs most commonly abused are opioids and central nervous system depressants (sedatives and tranquilizers) and stimulants (prescribed for attention-deficit hyperactivity disorder, narcolepsy or obesity).*[3]

Sponsors developing these types of compounds should plan studies to test for their abuse potential. These studies, referred to as Human Abuse Liability (HAL) studies, require more time and resources than most Phase I studies. The following pages review what sets these studies apart and presents, at a high level, what sponsors should be factoring into their trial plans.

Figure1.



THE IMPORTANCE OF STUDYING ABUSE

A drug's ability to produce rewarding psychoactive effects is considered predictive of the likelihood that it will intentionally be used in non-medical situations—despite labeling restrictions and being scheduled as a controlled substance.[4] Thus, such assessments are important initiatives for public safety.

In the U.S., HAL studies are required by regulators for new molecular entities that could have a "stimulant, depressant, or hallucinogenic effect on the central nervous system"[5] and that would fall under the Controlled Substances Act (CSA) of 1970. They are also required for marketed drugs that surface an unexpected safety profile, such as when adverse event reports raise questions about the drug's mood altering effects. The U.S. Food and Drug Administration (FDA) published guidance on assessing drugs' abuse potential in 2010.

Determination of a drug's abuse potential is based on a number of factors taken together, including its chemistry and pharmacology, clinical uses, and public health risks. HAL studies are designed to measure a subject's experiences of euphoria, hallucinations, perceptual and other cognitive distortions, and mood changes. Generally, more than one study is required to assess a drug's abuse potential adequately.

The targeted drugs that affect the central nervous system include:

- Opioids
- Depressants
- Stimulants
- Hallucinogens
- Cannabinoids
- Nicotine-like drugs
- Anabolic steroids
- Certain compounds in at-risk indications such as ADHD and anxiety

The U.S. Drug Enforcement Administration (DEA) categorizes drugs into five schedules based upon their medical use and abuse potential. Schedule II drugs—those with valid medical uses but with high potential for abuse—include: cocaine, methamphetamine, methadone, hydromorphone (Dilaudid®), meperidine (Demerol®), oxycodone (OxyContin® and Percocet®), fentanyl (Sublimaze® and Duragesic®), morphine, opium, codeine, amphetamine (Dexedrine®, Adderall®), methamphetamine (Desoxyn®), methylphenidate (Ritalin®), amobarbital, glutethimide, and pentobarbital.

A Word on Definitions

Drug Abuse: The World Health Organization (WHO) defines drug abuse (or misuse) as "persistent or sporadic excessive drug use inconsistent with, or unrelated to, acceptable medical practice."

Addiction: According to the American Society of Addiction Medicine, "Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.[6]

Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death. [7]

Dependence: In the International Classification of Diseases and Health Problems (ICD-10), the dependence syndrome is defined as "a cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take the psychoactive drugs (which may or not have been medically prescribed), alcohol, or tobacco."[8]

Abuse Potential: Finally, a drug's abuse potential is evaluated based on several factors, including its properties, effects, use, and diversion history. In the U.S., eight factors are to be considered when determining if the Controlled Substance Act (CSA) should apply to a drug:

1. Its actual or relative potential for abuse
2. Scientific evidence of the drug's pharmacological effects
3. The state of current scientific knowledge regarding the drug or other substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Its psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled.

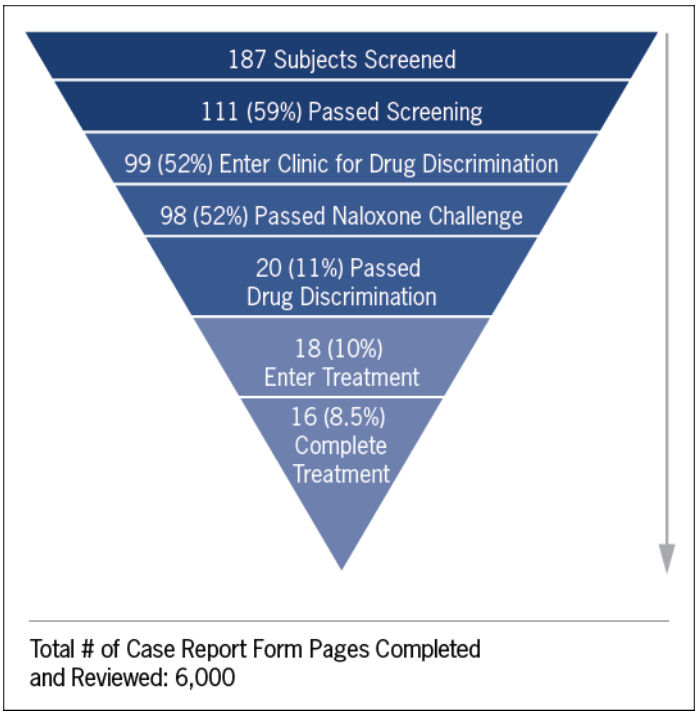
THE GENERAL RESEARCH APPROACH TO HAL STUDIES

While each study to test human abuse potential is unique, as a whole, they are generally randomized, double-blind, double-dummy studies with a placebo or positive comparator used as a control. They usually involve a dose given to multiple cohorts of recreational drug users through a crossover design.

Recreational drug users are the preferred subjects for two reasons. First, they represent the population at greatest risk for abusing a drug once on the market. Second, their experience with recreational drug use enables them to "provide meaningful ratings of their drug experiences in the lab."[9] FDA guidance on the topic notes, "…some abuse potential studies have also been conducted in drug naïve healthy subjects, and this is an area of needed research" since the two populations may differ, especially in their ability to differentiate the effects of drugs.[10]

The FDA's guidance states that HAL studies, which are challenging because of the subjective nature of the assessments and the subject population, should be conducted under controlled laboratory settings. Ideally, the setting provides a closed residential unit that would allow the subjects to stay overnight following the administration of each dose.[11] At present, there are only a select few sites in North America equipped and staffed to handle HAL studies.

Figure 2: Subject Counts by Phase of a Sample HAL Study



Screening

As a first step, subjects undergo a standard screening assessment to include the collection of their medical history and selected laboratory assessments. Subjects presenting with a current diagnosis of substance dependence or currently being treated for a substance-related disorder are excluded from participation.

Naloxone Challenge

Subjects that pass the initial screening must undergo another screening test to ensure that they are not suffering from a physical addiction to opioids. During an overnight visit to the clinic, volunteers are given a small dose of Naloxone, which reverses the effects of a narcotic, and then are evaluated for signs of withdrawal using the Clinical Opiate Withdrawal Scale (COWS). If no symptoms of withdrawal are apparent with this initial dose, often a higher dose is then administered. Subjects that still display no symptoms of withdrawal are deemed free of a physical addiction and fit to continue to the next stage of the research.

Drug Discrimination Test

For the HAL research to be valid, "Study subjects should be able to distinguish the effects of the test drug and similar drugs and should be able to demonstrate that they can discriminate the effects of the positive control from the placebo."

Thus, before subjects are approved for participation, they are tested to see if they can tell whether they've been administered a placebo or a comparator product known to have abuse potential. (Ideally, the drugs used as positive controls are in the same class of drugs as the compound under study and target the same indication.) Subjects unable to discern the difference between similar compounds or placebo are screened out. Those subjects who were sensitive to the difference between placebo and the comparator drug (and sometimes to different doses of the comparator drug) are then approved for participation in the treatment phase of the HAL study. Again, subjects are kept overnight in the laboratory for the drug discrimination test.

Investigators performing the drug discrimination assessment must be familiar with the assessments used in HAL studies. Subjects should be given training and practice on how to complete the assessments appropriately before taking the actual test.

It is quite common for there to be a high screen failure rate for HAL studies, largely because of the drug discrimination phase. Some studies have had screen failure rates of as much as 80 percent. The potential for screen failure increases with the number of comparator drugs and doses tested.

Treatment Phase

It is advisable to begin the actual study only after all of a subject's results have been analyzed and monitored. As with the Naloxone challenge and the drug discrimination phase, subjects are kept in the clinic overnight for observation when the study drug is actually administered.

Following the administration of the study drug, placebo or comparator, subjects are evaluated via a battery of measurement tools, including the clinician's observation; self-completed, standardized questionnaires; and investigator-administered tests, all of which have validated rating scales. These may include:

- Ratings of liking (via the Visual Analogue Scale, VAS)
- Disposition to take the drug again
- Drug identification, meaning able to categorize the effects as similar to other classes of drugs
- Measurement of physiological effects (Pupillometry, Cold Pressure Test)
- Behavioral and cognitive performance
- Drug Effects Questionnaire (DEQ)
- Assessment of mood state changes using Profile of Mood States (POMS) and the Addiction Research Center Inventory (ARCI)

Given the specialized nature of these assessments, it is important to work with experienced investigators who have been trained in, and have experience with, such tools.

INHERENT CHALLENGES IN MANAGING HAL STUDIES

Population Challenges

The study population can present some challenges beyond those seen in other types of studies. As a general rule, these volunteers are eager to participate in the study. Sites, however, may experience a number of "no shows" due to the nature of the study population. And as mentioned above, the screen failure rate can be extraordinarily high due to the inability to distinguish between similar compounds, different doses and placebo. Obviously, this has implications for recruiting timelines and monitoring workloads.

Researchers should be mindful of the fact that potential subjects may attempt to sign the consent form while under the influence of an abused substance, in which case their capacity to freely consent would be impaired. What is more, "tolerance to a substance may minimize a drug's effect on cognition, which is why testing for the presence or level of a substance [via the Naloxone challenge] cannot be the sole determinant of whether an individual has capacity or not. Alternatively, the judgment of potential subjects who have not taken a drug within their usual timeframe could be impaired by withdrawal.[13]

In addition to the usual best practices in ensuring informed consent within vulnerable populations, researchers may also need to[14] :

- Query the subject as to his or her understanding of what the study is about
- Obtain an independent evaluation from a qualified clinician, ethical consultant, or uninvolved third party
- Administer the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), a semi-structured, interview-based instrument

Since, when subjects apply to participate in HAL studies they admit to recreational drug use—a potentially illegal activity—sponsors must obtain a Certificate of Confidentiality (COC) ensuring that researchers will not disclose the subject's admission of drug use in any criminal investigation or legal proceeding.

Due to the nature of the research, subjects must be closely observed at all times, necessitating that the facility have a large and well-trained clinical staff.

Monitoring Challenges

Monitoring HAL studies is more time sensitive, labor intensive, and specialized than most other Phase I trials. This is the case because:

- HAL trials generate copious amounts of data, because so much information is gathered in the screening process and so many assessments are performed. All of this data must be validated and monitored.
- Subjects typically progress through the research in cohorts, so when this is the case, data from one stage must be reviewed before the cohort can proceed to the next phase of the study. This means that Clinical Research Associates (CRAs) must be on hand for intense periods of real-time monitoring so that cohorts can move to the treatment phase without delay.
- An unblinded monitor who understands Schedule II drugs must oversee the pharmacist's work. This unblinded monitor is charged with ensuring that the randomization schedule is followed correctly; that all drugs are properly accounted for to prevent diversion; that DEA 222 forms are in order; and that the drug was prepared and administered according to the protocol.

It is not unusual to require multiple fully dedicated CRAs to be on site throughout the duration of a HAL study—which is generally more than is required in most other Phase I studies.

Data Challenges

Since HAL studies incorporate additional levels of screening in the Naloxone challenge and the Drug Discrimination phase, each Case Report Form (CRF) involves significantly more pages of information than most Phase I studies. In many Phase I studies, only one or two pages of information may be collected in the CRF before the subject moves on to treatment. In HAL studies, the Drug Discrimination phase alone can generate 50 pages of information per subject..

To add to the challenge, the data are gathered over a short period of time and have to be entered and reviewed and cleaned quickly so that eligible patients can proceed to the treatment stage in a timely manner.

Communication/Coordination Challenges

Only a select few sites have the required facilities and expertise to conduct HAL studies, and coordinating with them is more than ordinarily critical to ensuring that the study progresses smoothly. To begin with, sponsors need to ensure that the sites know how to take the time to introduce subjects to the rating scales and systems they will be using.

The CRAs and unblinded monitor must be apprised of when each cohort is scheduled in a given phase so that they can be on hand to perform their duties and keep the process moving.

During the Drug Discrimination and Treatment phases, the site must carefully coordinate the timing and sequence of assessments, especially when multiple procedures coincide relative to dosing. For example, some assessments need to be completed within five minutes of drug administration.

Frequently with these studies, the determination of which subjects can move on to the treatment phase is made jointly between the Principal Investigator and the Medical Director. The CRO Project Manager can help by coordinating and facilitating these meetings to avoid undue delays in the process.

WHAT SPONSORS SHOULD KNOW

Conducting HAL studies is a specialized form of clinical research about which volumes can be written. Key points for sponsors to consider when planning such studies include:

- There is no single, standard assessment strategy that can be applied to all HAL studies. The types of assessments needed must be determined on a case-by-case basis, although there is a portfolio of available, validated tools that are well established.
- A customized monitoring plan can be developed by starting with a general format established for opioid HAL trials and then altering it as needed.

U.S. Regulatory Requirements for Handling Schedule II Narcotics

The manufacture, distribution and dispensing requirements for Schedule II narcotics (such as the opioids) are regulated in the U.S. by the Drug Enforcement Agency (DEA) of the U.S. Department of Justice. The regulations, as outlined in Title 21 of the United States Code (USC) Controlled Substances Act in the Office of Diversion Control, stipulate that research studies involving Schedule II products meet certain criteria and employ special forms and procedures.

In order to dispense controlled substances to research subjects, each participating PI/pharmacy must be registered with the DEA and have a current DEA 223 license. This license must be included in the essential documents provided for drug approval. Sites must store Schedule II narcotics in a secure, locked area of the pharmacy or clinic—within some containment device that cannot be easily removed from the premises. The CRA must verify during the Pre-Site visit that the site has provided for acceptable drug storage.

All shipments of controlled substances must be accompanied by a completed DEA 222 form. These forms are supplied by the DEA and must be completed by the person/pharmacy that is to receive the drug.Since DEA 222 forms expire 60 days after they are granted by the DEA, sites must monitor their inventory of current forms. To ensure an adequate supply of valid forms so that the site does not run out, they must factor in sufficient time to receive fresh quantities, or risk delays in receiving the necessary drug shipments. Sites should be trained on how to complete the DEA 222 form to avoid the types of errors that often cause delays in drug receipt. For instance, the address listed must match the *exact* location to which the drug will be shipped.

When drugs are returned, they must be accompanied by the Form DEA 222from the depot where the drug is being returned.

In conclusion, research studies involving Schedule II narcotics require additional forms and procedures in order to be regulatory compliant. Choosing a Contract Research Organization (CRO) with this specific type of experience will ensure that realistic timelines are set, that deadlines are met and that the study is conducted smoothly.

- The study population is generally young and healthy, and this should be reflected in the inclusion/exclusion criteria and screening standards. For example, it may be normal for subjects to present with very low blood pressure.
- HAL studies require heavy CRA involvement in monitoring and data cleaning. Sponsors should be prepared for the need to assign more resources than is typical for other Phase I trials.
- HAL studies necessitate the collection of many pharmacokinetic samples from each subject, and due to the acute nature of the drug administration, cannot be re-collected should something go wrong in the handling process. Therefore, sites should be fully trained in sample handling and shipment procedures and this process should be closely monitored by the CRAs.
- Scheduling for the smooth progression of the trial under optimal timelines is challenging. The site and the CRO need to work together closely on the timing of recruitment, which can take longer than in other types of studies. And, they must coordinate their schedules around cohort start dates to ensure that monitoring visits coincide.
- Data entry and monitoring is more than usually time sensitive. Because the findings of each stage need to be evaluated before subjects can move on in the trial, sites must keep up with data entry, and monitoring has to be done in real time.
- Sponsors need to budget more funds than usual when bidding HAL studies.
- The FDA encourages sponsors to interact closely with the agency in planning such studies.

CONCLUSION

HAL studies are a necessary part of drug development for CNS compounds with an abuse potential. They require specialized settings and knowledge and can be more challenging, costly, and labor intensive than traditional Phase I studies. Accordingly, sponsors should work with a partner experienced in planning and managing them to ensure that all aspects run smoothly and efficiently. In particular, there is a need for very close coordination between the study monitor and the site to ensure that patient activities and data collection and monitoring keep in lock step throughout the process.

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