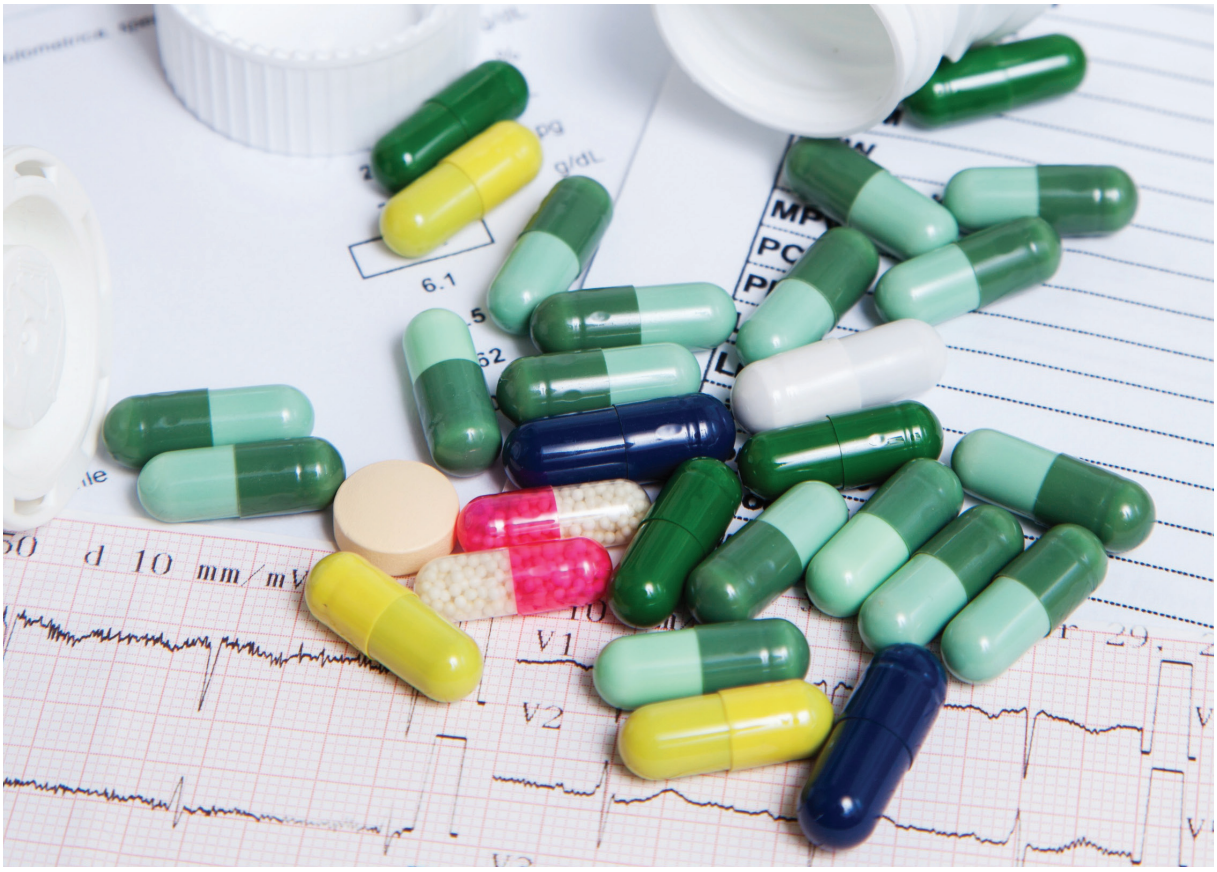

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Used and Abused

Delivering effective medication may be the end aspiration of the trial process, but sometimes there is a darker side as the drug falls foul to misuse and abuse. Now gaining more attention, human abuse liability studies of recreational drug users aim to tackle this

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Human abuse liability (HAL) studies are currently receiving substantial interest across the pharmaceutical industry after the FDA issued two draft guidance documents: *Assessment of abuse potential of drugs* in 2010 and *Abuse-deterrent opioids – Evaluation and labeling* last year.

According to the FDA, the 2010 draft guidance "is intended to assist sponsors who are developing drug products with the potential for abuse that may need to be scheduled under the Controlled Substances Act (21 USC 811(b), 811(c)). Examples of products that are addressed in this guidance include new molecular entities and new dosage forms of drug substances already controlled under the Controlled Substances Act (21 USC 812(c)). Drugs with abuse potential generally include drugs that affect the central nervous system, drugs that are chemically or pharmacologically similar to other drugs with known abuse potential, and drugs that produce psychoactive effects such as sedation, euphoria, or mood change" (1).

The 2013 draft guidance "is intended to assist sponsors who wish to develop formulations of opioid drug products with potentially abuse-deterrent properties (abuse-deterrent formulations). Specifically, the guidance explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies will be evaluated, and what labeling claims may be approved based on the results of those studies" (2).

HAL Overview

HAL studies for new chemical entities (NCEs) are conducted to help understand if a new drug is 'liked', compared to a known drug of abuse in the same drug class or with a similar mechanism of action. In other instances, companies are required to evaluate the effectiveness of an abuse-deterrent formulation (ADF).

For ADF studies, the objective is to assess whether a new opioid formulation, which is designed to deter abuse, is 'liked' less than the original formulation that does not have abuse-deterrent properties. The assessment of ADFs is often in accordance with a 505(b)(2) strategy (an FDA drug development pathway).

Opioid Epidemic

The 2013 FDA guidance was developed in response to the high rates of prescription opioid abuse plaguing the US over the last decade. Opioids are still considered to be the most effective medication for patients suffering from acute or chronic pain, and sales in the US have surpassed $10 billion a year (3,4).

Although opioids may be the most effective treatment option for pain patients, they are associated with serious side-effects, such as respiratory depression, sedation, and a high potential for abuse and addiction. The US Centers for Disease Control and Prevention released a report in 2010 showing that the number of emergency room visits for the non-medical use of opioid analgesics increased 111% from 2004 to 2008 (5). The number of persons 12 years or older who were current, non-medical pain reliever users in 2012 was over 4.9 million, while the figure for stimulant users was 1.2 million, and methamphetamine users was 440,000 (6).

Scheduling and Labelling

HAL studies designed to assess NCEs help to determine a drug's potential for misuse or abuse. The data collected can support a label claim, in addition to guiding the development of risk strategies post-approval. Ultimately, the US Drug Enforcement Agency recommends a schedule for an NCE as part of the new drug application process with the FDA. The schedule for the NCE is a significant determinant behind the potential commercial success of the product and plays a broad role, from manufacturing and distribution control to reimbursement and marketing.

In short, the labelling derived from data obtained from the HAL study – taken as a whole with other preclinical data – can determine the fate of the drug and, to some degree, the sponsor company, making this clinical pharmacology study pivotal to the strategy of the overall submission.

Recreational Drug Volunteers

HAL trials present a unique set of challenges, compared to other Phase 1 clinical pharmacology studies. The main differentiator is that HAL studies require the participation of recreational drug users, as opposed to healthy normal volunteers or patient volunteers.

Such studies evaluate the responses of healthy individuals who are recreational drug users to a battery of predefined visual analogue scales (VAS), administered on paper and now often via cloud-deployed cognitive testing systems. The typical tests include endpoints such as 'drug liking', 'take drug again' and 'overall drug liking', among others specific to the drug under investigation.

A qualification phase, in which study volunteers demonstrate the ability to differentiate effects between placebo and a comparator drug, is strongly recommended to provide face validity and reduce the risk of false negatives (7).

The recruitment and retention of study volunteers who both meet the inclusion/exclusion criteria of the protocol and can differentiate between placebo and the active comparator, can pose difficulties. It is not uncommon at certain clinical pharmacology units for over half of study volunteers who meet screening criteria to not correctly discriminate comparator drug from placebo during the qualification phase; or, for a host of reasons, to not demonstrate a time-course appropriate response to the positive drug. A high fail rate at screening and qualification can lead to longer screening periods and higher costs for the sponsor.

Operational Success

Principal investigators (PIs) who are experienced in recruiting and retaining recreational drug users are essential for the successful execution of these types of studies. These PIs have clear insight into the study design components that are most likely to result in the successful completion of a HAL study. An experienced PI and clinical team routinely work with sponsors to improve their protocols, so there is a high likelihood of success from an operational perspective.

The operational aspects that are included in an effective HAL protocol – leading to effective recruitment and retention – are multifactorial and complex. The study objective hinges upon the ability of the subject to respond appropriately to the drug comparator versus placebo; therefore, a number of operational strategies should be implemented to ensure that the highest quality data is obtained from the study.

The population of recreational drug users necessitates that the site is equipped to medically monitor and safeguard their study volunteers, as well as gather appropriate data in support of the trial. As the administration of controlled drugs is required, it is imperative that the study team is composed of experienced healthcare professionals and that emergency facilities are in close proximity.

In addition, secure drug storage is necessary to ensure drug control and the safety of all participants. Pharmacies should have significant investment in secure drug storage areas, including strict access control – for example, keycard entry and facial recognition systems.

Study volunteers under the influence of the administered drug require well-trained staff to support them during assessments. Appropriate training of VAS for study volunteers by experienced staff is pivotal in the successful execution of HAL trials.

Recruitment Caveats

Faced with multiple study requests, clinical pharmacology units may be tempted to enrol similar studies at the same time. Sponsors should request that the unit provide feedback on recruitment, based on the expectation that their individual study will be the sole focus of recruitment efforts in the chosen comparator class.

Recruiting more than one study in the same class of experienced recreational users may effectively 'cannibalise' competing studies, and should be avoided where possible. Moreover, ensuring volunteers are familiar with not only the class of drug under study but also the route of administration is important. Operationally, this means that volunteers experienced in assessing subjective effects of the study drug when taken via their preferred route of administration (for instance, oral) may not be able to accurately rate the same effects when the route of administration differs from their experience (for example, insufflation).

Volunteers lacking experience in different routes of administration for drugs may lead to an unclear response and confounding data interpretation. This is best avoided by using a well-characterised group of study volunteers from a verified and current database, as well as specific inclusion/exclusion criteria.

Endpoints and Data

The study endpoints are significant determinants in the operational success of HAL studies. During the design phase, the head biostatician works with the clinical pharmacology site and the sponsor to ensure that the study is appropriately powered, to clearly demonstrate a detectable difference between placebo and the active comparator on subjective effect responses. Numerically, a typical HAL trial will enrol between 30-40 study volunteers.

From a logistics perspective, the various endpoints are carefully considered to limit the number of VAS scales administered in order to avoid rater fatigue, which can occur when too many scales are required for study volunteers to complete and the subject becomes less reliable. This allows for more appropriate responses from the subject and ensures that the best possible data is collected.

Logistical Considerations

Trial logistics are important to study volunteers who are considering participating in a HAL study. Many of the volunteers have psychosocial issues that may limit their ability to participate in and complete the trial. Components such as duration of stay, the number of arms and the number of return visits drive the recruitment parameters for these studies.

It is recommended to conduct HAL studies at a closed, residential unit. Confinement reduces the risk of volunteers using prohibited medications, including drugs of abuse, and also reduces drop-outs and missed visits. Factors such as the potential for positive drug screens, concomitant medications and smoking need to be addressed in the protocol to balance study retention with quality data.

Smoking – commonly an exclusion criterion in most clinical trials – is an activity in which most substance users are actively engaged, and would pose a significant hurdle to enrolment if not permitted in HAL studies. The protocol inclusion criteria can be crafted to provide a maximum daily intake of cigarettes, with the site responsible for the access to the cigarettes and a secure smoking area provided for the volunteers.

Better Choices

The complicated regulatory pathway for HAL protocol design (comparator, recruiting, etc) requires individualised consulting for each case, and an experienced team to create and review the strategy. Overall, the best choice a sponsor can make is selecting a clinical pharmacology unit with experience in the logistics, operational conduct and interpretation of results for abuse liability studies, as well as access to the recreational drug using population.

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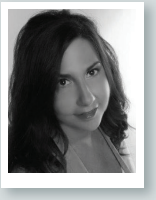
About the author



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