



Lotus CLINICAL
RESEARCH® LLC

Better Science. Superior Results.

Analgesic CRO **and Research Site**

CRO and Research Site focused on improving the scientific accuracy of analgesic programs. Better Science. Superior Results.

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About Lotus Clinical Research

We are a specialty analgesic CRO and Research Site that supports all phases of discovery for novel analgesics and focuses on improving the scientific accuracy of analgesic programs.

As analgesic experts, we have a proven track record of conducting successful, full-service analgesic studies from startup through all phases of analgesic clinical trials.

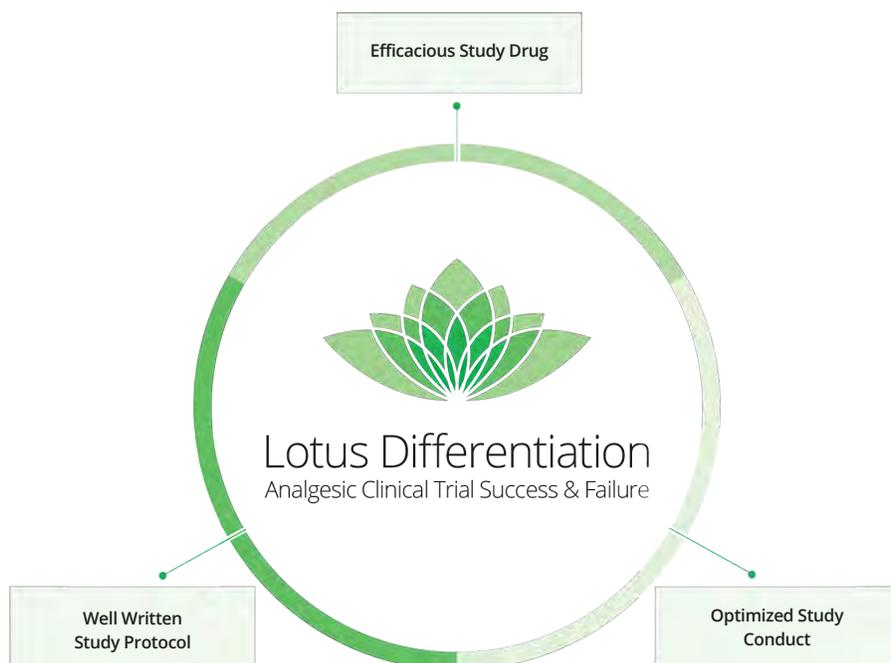
Led by Chief Scientific Officer Dr. Neil Singla, Lotus Clinical Research has assisted in the delivery of hundreds of innovative solutions for patient care in pain management since 2001.

Our Vision

To lead the CRO and site services pain market by inventing and validating scientific technologies that improve analgesic study design and conduct.

Our Mission

To succeed by providing value to our clients and society. For clients, Lotus Clinical Research seeks to invent and operationalize research methods that improve the efficiency of analgesic trials. For society, Lotus hopes that these improved research methods will facilitate the discovery of novel analgesics that reduce prescription drug misuse and abuse.





Our Founder

Neil Singla, MD
Chief Scientific Officer

Dr. Neil Singla, a board-certified anesthesiologist, is the founder and Chief Scientific Officer of Lotus Clinical Research. Since its inception in 2001, Dr. Singla has served in several roles within the organization including: Research Coordinator, Sub-Investigator, Principal Investigator, Coordinating Investigator, and Chief Scientific Officer.

In his capacity as CSO for Lotus Clinical Research, Dr. Singla has had the opportunity to interact frequently with the FDA's Analgesics Division on behalf of clients and to play a significant role in guiding development strategies for dozens of putative analgesic agents.

In the company's 16-year history, Dr. Singla and Lotus Clinical Research have played a significant role in bringing several molecules to market.

Dr. Singla has published extensively and is a frequent lecturer for physicians, pharmaceutical companies, and medical research institutes throughout the country. He currently chairs the Analgesic Clinical Trials Shared/Special Interest Group at both the American Pain Society (APS) and the International Association for the Study of Pain (IASP). He chairs the annual APS Conference on Analgesic Clinical Trials (APS-CAT), which aims to help experts advance best practices in analgesic drug development.

The main focus of Dr. Singla's academic endeavors has been to analyze and understand how the inherent variability in subjective endpoint analgesic clinical trials can be minimized. As a result, he has developed novel techniques for patient education designed to minimize variability, reduce placebo response, and increase effect size.

CRO Services

A scientifically driven CRO model for your analgesic investigations.

As a leading analgesic CRO, Lotus Clinical Research offers a robust CRO infrastructure, program-wide scientific support, as well as extensive analgesic and pain-related expertise in a complete turnkey solution for clients.

Project Management

The Lotus Clinical Research project manager is the cornerstone of a successful program.

Lotus Clinical Research provides skilled project managers that are well suited to the needs of analgesic trials. With an average tenure of 10+ years in the industry, our project managers have considerable experience in pain trials, with a focus on leading studies to on-time completion with the highest quality data to support regulatory submissions.

Our project managers are highly effective at rapid startups. By leveraging Lotus Clinical Research's analgesic expertise and collaborative approach, from final protocol to first patient in, projects have been activated in as little as six weeks.

We apply classic project management principles to effectively meet timelines and project milestones by optimizing lines of communication. Our project managers will seamlessly function as an extension of your team from protocol development through delivery of the Clinical Study Report (CSR).

As your single point of contact, the project manager will lead your study in:

- **Timeline development and management**
- **Protocol and Informed Consent Form (ICF) development**
- **Study plan development**
- **Patient reported outcome diary development**
- **Site selection**
- **Vendor management**
- **Recruitment strategies for targeted populations**
- **Risk mitigation: includes identification, analysis, response, and quality control**
- **Monitor and site performance management**
- **Study team, Clinical Research Associates and clinical sites communication**



EDC & Data Management

Lotus Clinical Research's analgesic databases are Part 11 and Clinical Data Interchange Standards Consortium (CDISC) compliant with audit trail and other key quality features.

Our databases fulfill important baseline attributes while allowing for the specialized configuration required for analgesic report outputs, and are configured with the end goal in mind: appropriate calculation of analgesic primary and secondary endpoints.

Data management services include:

- **Analgesic database design**
- **Manual and automated data validation on entered data (our review focuses on typical issues with pain trials, such as rescue medication versus pain intensity and typical analgesic adverse events)**
- **Medical coding**
- **Electronic Case Report Form (eCRF) design using an internal template library of pain CRFs for streamlined build approach**
- **Rapid EDC development, implementation and management**
- **CDISC Study Data Tabulation Model (SDTM)**
- **Conversion services**
- **Online access to the system**
- **Custom reports tailored to each individual trial**
- **Management of third-party data (e.g. lab, pharmacokinetics [PK])**
- **Data cleaning, including query management and report/listings review**
- **Standard set of reports tailored to pain trials**
- **Serious Adverse Event (SAE) reconciliation**

When interim analysis is required, time is of the essence. Precise, well organized data output allows biostatisticians to efficiently access the information required by the interim analyses in a timely manner. We perform test exports and analyses of dummy, protocol-specific data well before interim analyses take place to ensure that any kinks can be ironed out prior to "crunch time."

Clinical Trial Monitoring

Lotus monitors are independent experts in clinical trial monitoring, data collection, data review and reporting.

Lotus Clinical Research monitors have experience with both outpatient and inpatient analgesic charting, including anesthetic records and surgical procedure notes. Monitors are also trained in placebo response reduction and the administration of analgesic questionnaires. Proprietary Lotus generated training tools allow them to efficiently pass this information on to site-level staff.

Lotus Clinical Research's select group of monitors dedicate themselves to providing an exceptional level of quality data review while thoroughly engaging themselves with study sites. Our monitors perform on-site clinical trial monitoring visits throughout the duration of the study to oversee the collection of data; review clinical laboratory results, source documentation and electronic/paper case report forms; use data queries to identify issues, which need to be resolved; and confirm regulatory compliance.

To ensure structural and procedural independence is maintained between our CRO and site, monitors report directly to, and are managed by, Lotus Clinical Research CRO project managers.

Our monitors:

- **Are experienced in Phase I-IV clinical studies**
- **Provide GCP-focused data review**
- **Are trained/experienced in analgesic clinical trials**
- **Provide flexible scheduling to ensure proper on-site time**
- **Provide fast turnaround time for site visit reports**

Site Selection

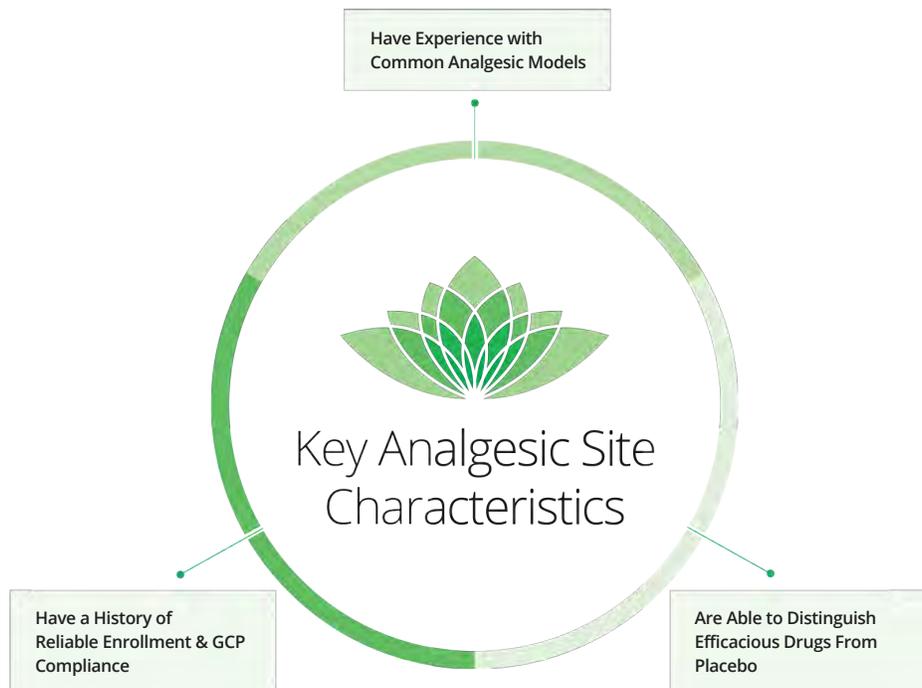
Lotus has worked repeatedly with sites that are experienced with common pain models.

As a result of specializing in analgesic research since 2001, Lotus has worked repeatedly with sites that are experienced with common pain models such as: dental extraction, bunionectomy, abdominoplasty, Delayed Onset Muscle Soreness (DOMS), Opioid Induced Constipation (OIC), knee replacement, hip replacement, soft tissue surgery, chronic lower back pain, osteoarthritis, postherpetic neuralgia, and Diabetic Peripheral Neuropathy (DPN).

To ensure site excellence, Lotus Clinical Research continually evaluates each site's performance, not only by tracking enrollment and assessing data quality, but also by quantifying scientific outputs. We only work with sites that have a proven track record of distinguishing efficacious drugs from placebo.

Some key analgesic site characteristics are:

- **Experience with common analgesic models**
- **Ability to distinguish efficacious drugs from placebo**
- **History of reliable enrollment and Good Clinical Practice (GCP) compliance**
- **Training site staff and investigators on minimizing placebo response**



Biostatistics

Our biostatistical staff members provide more than data analysis.

Our biostatistical staff members have in-depth knowledge of the methods for studying analgesic medications and the techniques that are used to analyze their results.

Lotus Clinical Research biostatisticians have years of experience processing and analyzing analgesic trial data. They have written numerous Statistical Analysis Plans (SAPs) and are distinctly familiar with the Division of Anesthesia, Analgesia, and Rheumatology Products' (DAARPs') position on analgesic data imputation, including MMRM, LOCF, BOCF, and WOCD, as well as more complex Rubin multiple imputation methods.

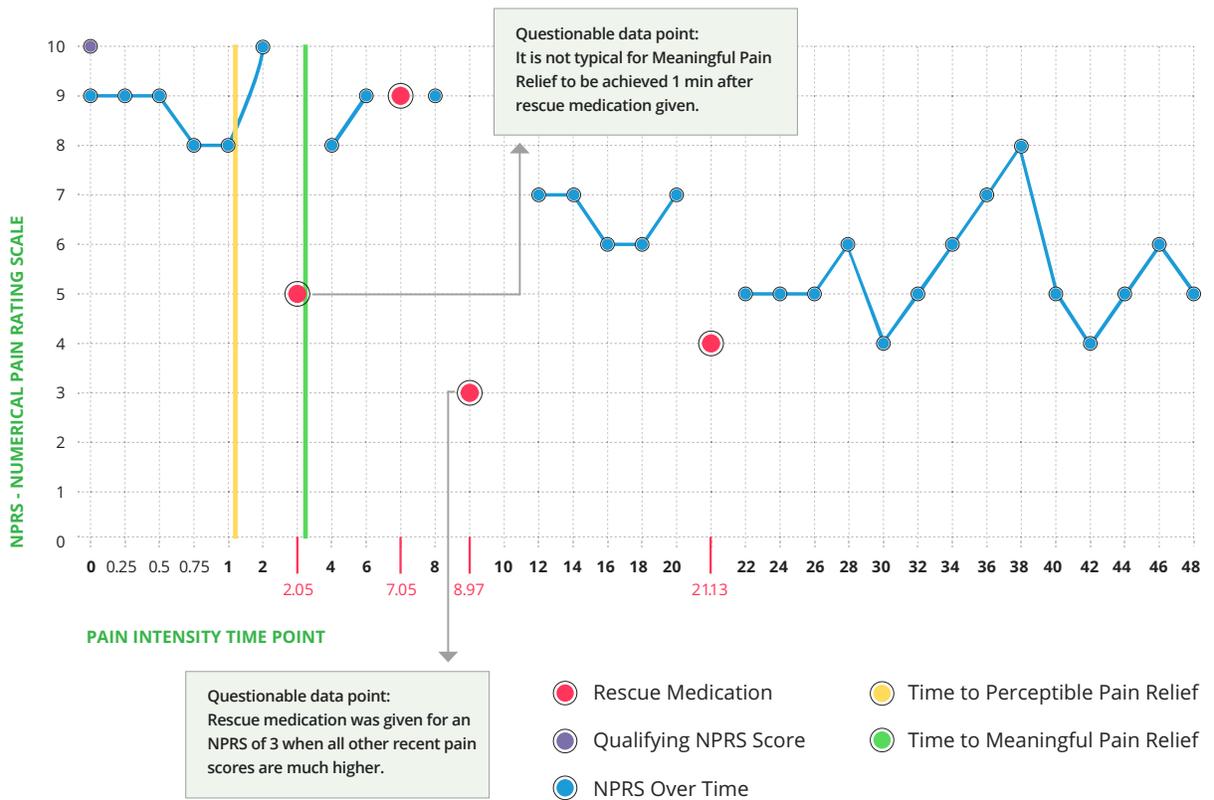
Our biostatisticians provide the following services:

- **Protocol review to assure appropriate study design and randomization, capture of important and well-defined endpoints, and use of pertinent statistical models and methods of analysis**
- **CRF and diary review**
- **Analgesic SAP generation with emphasis on appropriate data imputation methods**
- **Sample and effect size estimation based on literature review Interim analysis and Independent Data Monitoring Committee (IDMC) creation, management, and support**
- **Statistical programming and modeling**
- **Table, listing, and figure generation**
- **Statistical support for study reports (e.g. CSR, manuscripts, investigator's brochure [IB])**
- **Regulatory statistical consulting**

Pain Profile Reports

Lotus Clinical Research’s pain profile reports offer clear, early indicators of study volunteer readiness.

Below we demonstrate an example of one of our reports along with a few logical queries that might be generated. Understanding how sites are conducting analgesic studies in real-time allows problems to be identified during the open enrollment period (before it is too late).



Medical Monitoring

Patient safety is critical in clinical trials.

Lotus Clinical Research's team of experienced physicians and nurses is dedicated to providing a support network for our subjects. To provide this level of support, Lotus Clinical Research provides a 24-hour safety service for our clinical trials.

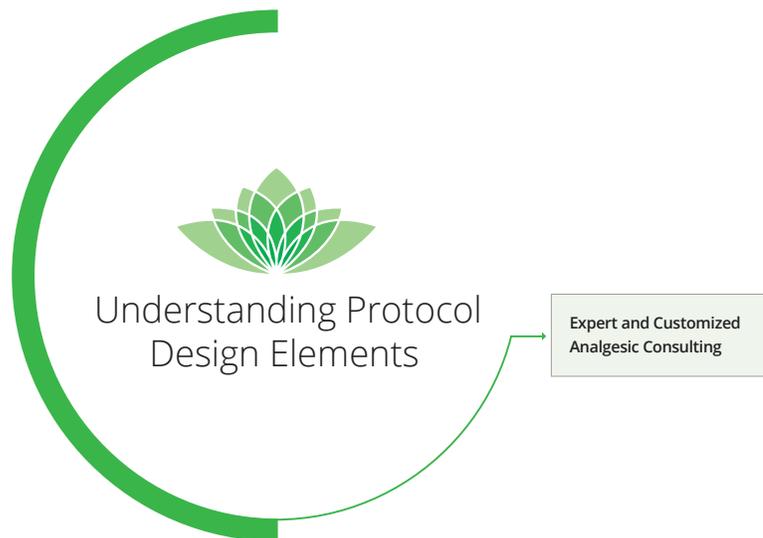
Analgesic trials provide a unique challenge because subjects who are enrolled generally have significant ongoing pathology (chronic disease states in the case of chronic pain trials and postsurgical morbidity in the case of acute pain trials). The medical monitors at Lotus Clinical Research are familiar with the natural pathophysiology of patients who enroll in analgesic trials, improving their ability to accurately survey these studies.

Medical Writing

Lotus Clinical Research's medical writers deliver accurate and timely documentation across every project.

Lotus Clinical Research medical writers are experienced in both clinical and regulatory writing techniques to provide concisely written documents that exceed client expectations.

Our writers work closely with our biostatisticians and peer reviewers to ensure documents are complete and faithfully represent our high level of scientific rigor and patient care. Moreover, Lotus Clinical Research's highly collaborative approach ensures well-formed documents that consider client preferences, local regulations, and guidelines.



Quality Operations

Our team provides study recommendations and improvements that support the safest and most efficient means of conducting trials.

Lotus Clinical Research's quality management team supports our internal teams and clients with the production of documents that comply with protocol and regulatory requirements. Our quality managers support the preparation of procedures, reports, and/or training materials that help safeguard study participants.

Our team provides study recommendations and improvements that support the safest and most efficient means of conducting trials while maintaining compliance with all local and regulatory guidelines. For multicenter studies, Lotus Clinical Research quality managers can utilize a team of highly experienced auditing professionals to conduct GCP-focused site audits to confirm site compliance to the protocol and federal regulations.

Ethics Management

Our ethics committee documentation services for sponsors ensures analgesic study quality, safety, and reliability.

Lotus Clinical Research provides ethics committee documentation services for sponsors. Our teams draw from extensive internal resources to provide the following services:

- **Quality review of startup documents**
- **Essential regulatory document collection from participating clinical trial sites**
- **Safety reporting**
- **Trial Master File (TMF) services**

Site Services

The team, expertise and resources for a faster time-to-market.

Lotus Clinical Research's pain research site is a private facility located inside a major metropolitan hospital in Los Angeles County. This provides our team and our clients with unprecedented access to state-of-the-art medical equipment and services, a large and ethnically-diverse population of subjects to recruit from, and a central IRB for rapid study starts.

Specialty Analgesic Services

We customize remote data capture and monitoring for logical data queries for analgesic protocols.

Most studies simultaneously capture multiple endpoints that should logically flow in different directions, such as an increase in pain relief or a decrease in pain intensity. We customize remote data capture and monitoring for logical data queries for analgesic protocols.

Sponsors can use our proprietary system to compare analgesic scales and ensure that sites are correctly capturing critical study endpoints, as well as evaluating rescue medication usage and patient dropout rates. Utilizing our blinded data monitoring tools, sponsors can identify and fix a study's methodical problems during (not after) the open enrollment period.

Our specialty analgesic services include:

- **Video education training for subjects on such topics as:**
 - **How to rate pain using NPRS**
 - **What is placebo?**
 - **Use of rescue medication**
 - **Double stopwatch technique**
 - **And many more**
- **Testing of subjects to evaluate their comprehension and need for further education regarding pain scales**
- **Collection of intermittent and continuous Cerebrospinal Fluid (CSF) samples**
- **Control for study co-founders**
- **Assurance of strict compliance with investigational product and rescue medication**
- **Ability to provide 24/7 critical care monitoring with an on-site anesthesiologist**

Unit Features

Lotus Clinical Research's facility provides extensive safety protocols, scientific oversight, and a broad range of ancillary study-related amenities.

Our facility offers unsurpassed safety protocols and scientific oversight, as well as comprehensive services specifically designed for volunteer participants and Lotus clients, including:

- **Outpatient clinic and multiday inpatient housing environment**
- **Private patient rooms with bathrooms just steps from the bed**
- **All rooms equipped with medical gasses and a nurse call system**
- **Customized meal service that can accommodate strict dietary restrictions**
- **Atomic clocks**
- **Around the clock nursing and medical coverage**
- **Network of physicians and surgeons from all specialties**
- **On-site emergency code team coverage**
- **Located upstairs from a Level 2 Trauma Center Emergency Room**
- **Multiple small and large conference rooms with internet access for CRAs**
- **Utilizes central IRB**
- **Around the clock security**

Pharmacy

On-site pharmacy services, with features and safety measures for ongoing analgesic research programs.

Lotus Clinical Research provides access to on-site pharmacy services at our facility, with features and safety measures that support ongoing analgesic research programs:

- **Double-locked narcotics room**
- **PCA and infusion pumps for drug administration**
- **Laminar flow hood**
- **Ambient and refrigerator storage with continuous remote temperature monitoring/alert system**

Lab & Specialized Equipment

Lotus Clinical Research is outfitted with flexible lab space and the latest in medical and scientific equipment to support even the most complex analgesic study.

Our provides access to on-site pharmacy services at our facility, with features and safety measures that support ongoing analgesic research programs:

These include:

- **Continuous capnography and pulse oximetry monitoring**
- **Multiple ECG machines**
- **On-site X-ray machine and direct access to all radiology imaging**
- **Expertise in PK draws**
- **Refrigerated and non-refrigerated centrifuge**
- **Minus 70-degree freezer with continuous temperature monitoring/alert system**
- **Delayed Onset Muscle Soreness (DOMS) exercise equipment for legs and arms**
- **Full-service surgical suite**

CSF Sampling

Lotus Clinical Research is able to perform specialized studies requiring CSF sampling.

Understanding the distribution of pharmaceutical agents in the central compartment is important for many pharmaceutical products. At Lotus Clinical Research, we have performed several studies that have required continuous or intermittent CSF sampling. Continuous sampling is achieved by placing a multi-orifice catheter in the patient's intrathecal space. Our team of experienced anesthesiologists have sampled and monitored patients continuously for up to 72 hours.

Placebo Response Mitigation

Specialized analgesia education and training for accurate results and outcomes.

Lotus Clinical Research has developed proprietary materials for patient education and staff training that consistently increase effect size by minimizing variability and placebo response in analgesic clinical trials. In addition, we provide an exclusive placebo response education series designed to modulate patient expectations and mitigate placebo response.

Placebo Response Videos

Lotus Clinical Research is outfitted with flexible lab space and the latest in medical and scientific equipment to support even the most complex analgesic study.

Lotus Clinical Research has developed a proprietary placebo response video education series designed to modulate patient expectations and dampen placebo response. This video series equips patients with important information about an analgesic trial's purpose, as well as what to expect throughout the duration of a study.

Through this series, patients receive placebo response education across the following areas:

- **Understanding the terms placebo control and double-blind**
- **What is the placebo effect?**
- **The difference between a treatment relationship and a research relationship**
- **How to rate your pain consistently using pain scales**
- **Measuring pain on a Visual Analog Scale (VAS)**
- **Numerical Pain Rating Scale (NPRS)**
- **Collecting pain relief assessments**
- **Measuring pain relief using the two-stopwatch technique**
- **What is rescue medication**

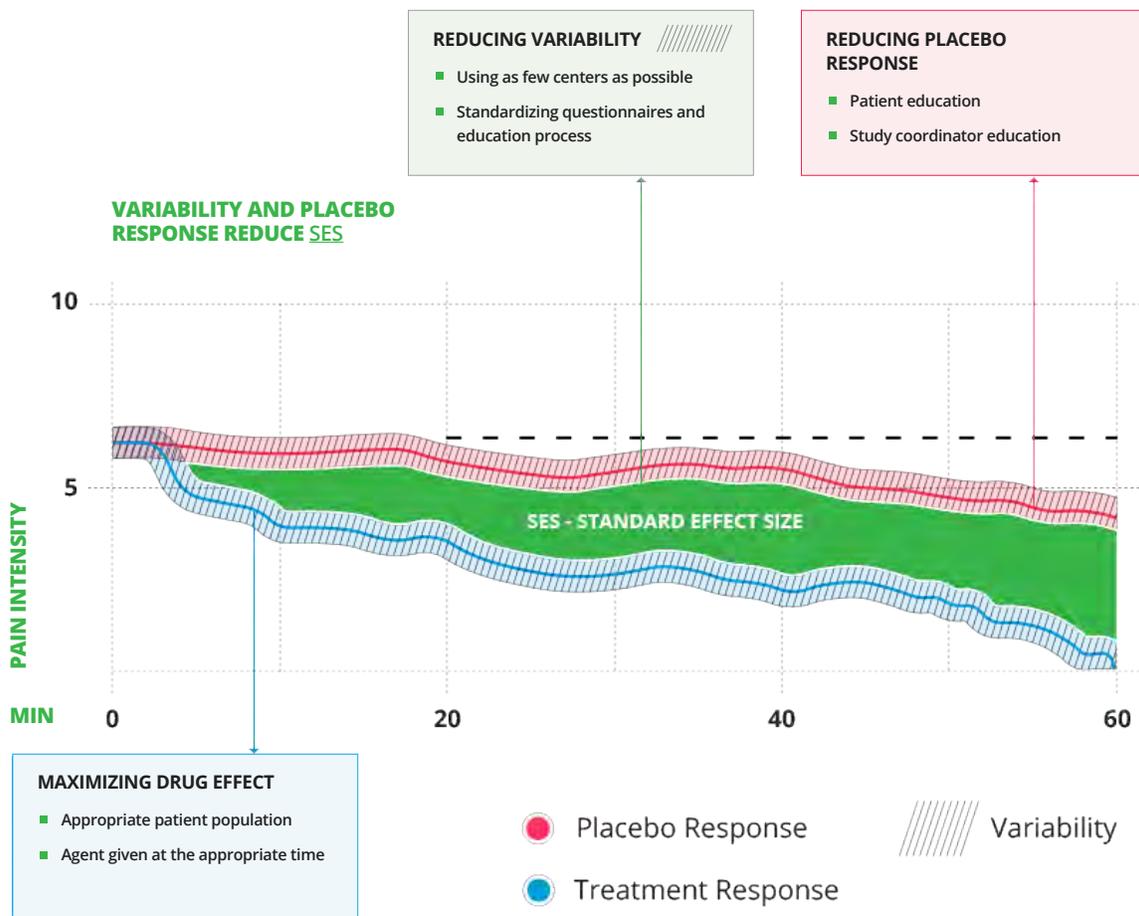
Maximizing Effect Size

The specialized experience and guidance to maximize assay sensitivity.

At Lotus Clinical Research, we have spent years honing our clinical trial skills in order to minimize variability and reduce placebo response in our investigations.

At our research site in Pasadena, California, Lotus Clinical Research has developed subject and staff education packages designed to maximize assay sensitivity. We have successfully deployed these educational programs in numerous multicenter investigations through our CRO.

By reducing variability and placebo response, Standardized Effect Size (SES) is maximized. Lotus Clinical Research provides the experience and guidance necessary to design and execute study protocols that will have high assay sensitivity.



Staff Training

Properly educated staff can stabilize patient expectations and reduce placebo response.

At Lotus Clinical Research, we believe that following the protocol is only the beginning of our responsibility. Subjective endpoint clinical trials require finesse and critical thinking that move beyond a robotic examination of protocol-mandated duties.

All members of our staff are required to understand the primary endpoint of each investigation and its method of calculation so they can focus their efforts on obtaining non-biased and accurate data.

Sample of our Clinical Vignettes:



**CLINICAL VIGNETTE
FOR PERI-OPERATIVE PAIN TRAINING**

Lotus uses several clinical vignettes as part of our peri-operative pain staff training. Below is one example:

Assume the following conditions are true for this hypothetical protocol:

- Post-operative randomization is allowed when the patient has a pain score greater than 4/10 on a visual analog scale and has at least moderate severity on a 4 point categorical scale (0=none, 1=mild, 2= moderate and 3=severe).
- Pre-randomization criteria states that the patient's peri-operative pain must be stable.
- This is an efficacy study with the main efficacy goal being separation of active drug from placebo.

Case # 1) 26 year old female presents for laparoscopic cholecystectomy. Surgery and anesthesia are uneventful. No protocol violations have occurred intra-operatively. Patient enters the recovery room and is clearly agitated. She is difficult to control in the recovery room bed, moving and writhing. Speech is garbled. She reports her pain as 9.5 on a 10 point scale. Her heart rate is 105.

Should the patient be randomized and study medication be administered at this time? Why or why not?

1b) Study staff decides not to randomize and instead to provide the patient with 25 micrograms of IV fentanyl for stabilization of her peri-operative pain. The fentanyl is administered at 8:05 AM. The protocol mandates a 20 minute waiting period after standard of care narcotics prior to reassessment for randomization. At 8:27 AM, the patient is queried as to her pain level. She is now resting comfortably, she says she is doing much better and the pain is subsiding. Her pain score is now 5/10 and moderate in severity. The protocol mandates that the pain must be at least 4/10 and moderate to severe.

Should the patient be randomized at this time? Why or why not?

Subject Education

As a study partner, the properly educated patient can be your greatest ally in avoiding falsely negative results.

A significant portion of an analgesic investigation's variability is produced secondary to cognitive gaps the patient may have when interpreting various protocol-mandated scales and questions. All pharmaceutical companies spend a large amount of time perfecting their protocol and selecting/educating quality sites; however, an equal amount of effort is rarely placed on patient education.

At Lotus Clinical Research, we believe this piece of the puzzle is the responsibility of the CRO and necessitated the development of proprietary educational materials, including a patient education video and a detailed patient post-test.

The Lotus Clinical Research Subject Education Program:

- **Provides a proprietary two-step process for subject education, including a 14-minute video and a tailored patient post-test.**
- **Demonstrates an increase in our effect size, and as such, confers additional statistical power to our pharmaceuticals clients.**
- **Focuses on key concepts, such as understanding protocol mandated analgesic scales, understanding the difference between a treatment relationship and a research relationship, and embracing the concepts of placebo control and double-blind.**
- **Prepares subjects for an analgesic post-test, which is designed to identify any cognitive gaps that the subject may have regarding the protocol-mandated analgesic scales and/or their role as an unbiased study participant.**

Analgesic Expertise

The experience and focus for developing innovative analgesic solutions.

Lotus Clinical Research has a deep understanding of the unique pathologies of pain syndromes, enabling us to develop comprehensive analgesic pain models specifically tailored to client needs, project requirements, and providing successful study outcomes.

MODEL	ASSAY SENSITIVITY	EFFECTS SIZE	REQUISITE N
CHRONIC PAIN MODELS:			
Osteoarthritis	Fair	0.45	170
Low back pain	Fair	0.45	170
Diabetic peripheral neuropathy	Poor	0.3	352
Postherpetic neuralgia	Poor	0.3	352
ACUTE PAIN MODELS:			
Third molar extraction	Excellent	1.4	30
Bunionectomy	Good	0.8	50
Abdominoplasty	Good	0.8	50
Total joint replacement (knee/hip)	Fair	0.6	90
Visceral surgery (hysterectomy/hernia)	Poor	0.4	200

SCALE	
1	Most Favorable
2	
3	
4	Least Favorable

Acute Pain Models

The advanced models necessary for rapid recruitment and reliable results.

Lotus Clinical Research has developed an acute pain model that offers numerous advantages over traditional models, providing clients with active engagement and recruitment of study subjects, on-site accessibility of surgical and recovery services, and lowered project costs throughout a study's lifecycle.

Abdominoplasty

While the bunionectomy is the gold standard for acute pain experiments in boney surgery, for many years there was no soft tissue equivalent to a bunionectomy (a rapidly recruiting, reliable, experimental soft tissue model with good assay sensitivity). Mindful of this experimental gap and market need, Lotus Clinical Research developed and validated the abdominoplasty model after years of study and pilot work. For abdominoplasty trials, Lotus Clinical Research provides both site and CRO services. Not only can we perform single-center abdominoplasty studies at our facility, but we also utilize a network of four well-vetted sites throughout the country for multicenter investigations.

The key to success in abdominoplasty research is minimization of variability and placebo response. To accomplish this, our CRO and sites utilize the Lotus Clinical Research subject placebo response education toolkit. This toolkit has been successfully deployed when our organization serves as a single abdominoplasty center and/or in multicenter abdominoplasty trials in which Lotus Clinical Research serves as the CRO.

The abdominoplasty model has attributes that make it a superior choice to other soft tissue models (such as laparoscopic cholecystectomy, hysterectomy, and herniorrhaphy), namely:

- **Rapid, reliable enrollment guided by advertisement.**
- **A significant surgical insult which results in adequate pain trajectory against which experimental agents can demonstrate assay sensitivity. Smaller soft tissue surgeries, such as laparoscopic cholecystectomy, have a minimal pain signature and, as such, poor assay sensitivity.**
- **Variability reduction secondary to a standardized anesthetic regimen and surgical technique.**

Enrollment results

Average enrollment is 40 subjects per month at the Lotus Clinical Research site. Screen failure rates average from 15-20 percent based on specific inclusion/exclusion criteria and the surgeon's assessment.

PHASE	SPONSOR	ENROLLED BY LOTUS	TOTAL STUDY IN	CLINICAL TRIALSGOV NO
2	Trevena	200	200	NCT02335294
3	AcelRX	47	102	NCT02356588
3	Grifols	40	120	NCT01731938
3	Grifols	9	120	NCT01731938

Bunionectomy

As a CRO and research site, Lotus Clinical Research is nationally recognized for its experience and proficiency in bunionectomy research.

For bunionectomy trials, Lotus Clinical Research provides both site and CRO services. We can perform single-center bunionectomy studies at our facility. When a multicenter environment is required, Lotus Clinical Research utilizes a network of five well-vetted, geographically diverse bunionectomy sites.

The key to success in bunionectomy research is minimization of variability and placebo response. To accomplish this, our CRO and site utilize the Lotus Clinical Research subject placebo response education toolkit. This toolkit has been successfully deployed when we serve as the single bunionectomy center and/or in multicenter bunionectomy trials when Lotus Clinical Research serves as the CRO.

Efforts are made to reduce variability among subjects in multicenter experiments by homogenizing the::

- **Surgical techniques: first metatarsal Austin bunionectomy without collateral procedures**
- **Anesthetic technique: Propofol sedation with mayo block; procedure performed with or without popliteal block depending on protocol requirements**
- **Recovery room procedures: standardized analgesic regimens, avoidance of ice, ambulation disallowed**
- **Inpatient stay: private rooms, comingling discouraged, restricted ambulation, no visitation from family or friends.**

Enrollment results

Average enrollment is 30 randomized subjects per month at the Lotus Clinical Research site. Screen failure rates are typically low, but are dependent on the specifics of the clinical protocol and its inclusion/exclusion criteria.

PHASE	SPONSOR	ENROLLED BY LOTUS	TOTAL STUDY N	CLINICAL TRIALS GOV ID.
2	Heron	53	100	NCT02471898
2	AcelRX	50	110	NTC01710345
2	Recro	50	150	NTC02284243
3	Covidien	89	320	NCT01484652
3	Covidien	89	320	NCT01743625
4	Regenesis	70	300	NCT01694199
3	J&J	155	897	NCT00613938
3	Teva	53	560	NCT02487108

Delayed Onset Muscle Soreness

Delayed Onset Muscle Soreness (DOMS) is an acute pain state that arises 24-48 hours after unaccustomed or eccentric exercise. As an analgesic model, it is well suited for testing topical over-the-counter or prescription analgesics.

Lotus Clinical Research has performed several large-scale studies (operating as both a site and the CRO) in the DOMS model. Dr. Singla has also published a methodological review article in PAIN concerning experimental best practices for DOMS.

PHASE	SPONSOR	ENROLLED BY LOTUS	TOTAL STUDY N	CLINICAL TRIALS GOV ID.
4	Lotus	144	144	NCT02087748
3	Novartis	102	102	NCT02271854
2	Aponia	144	144	NCT02324985

Joint Replacement Surgery

Lotus Clinical Research has extensive experience in the joint replacement model both as a CRO and as a research site. We can perform single-center joint replacement studies at our facility, and we also utilize a network of six well-vetted sites throughout the country for multicenter investigations.

Total joint replacement (total knee and/or total hip replacement) is a good analgesic model when sponsors are seeking study results that will have a high degree of clinical relevance.

Bunionectomy studies enroll more rapidly and have higher assay sensitivity than studies performed in joint replacement. However, joint replacement studies are generally well accepted by the medical community because they are considered to be clinically relevant to physicians who ultimately prescribe acute pain drugs (orthopedic surgeons, anesthesiologists, and general surgeons).

Lotus Clinical Research has implemented the following key success factors in previous joint replacement trials:

- **Selection of sites with a history of reliable enrollment**
- **Consensus building among surgeons and anesthesiologists regarding an acceptable regimen of perioperative medications**
- **Standardization of ancillary hospital services that tend to confound analgesic results (physical therapy, continuous passive range of motion devices, early ambulation protocols, and nerve blocks)**
- **Placebo response training for study subjects and research staff**

Enrollment results

Lotus Clinical Research is located inside of Huntington Hospital, which is a large tertiary care center with a high volume of orthopedic surgeries. As such, Lotus Clinical Research has long standing relationships with multiple orthopedic surgeons and anesthesiologists within the hospital. This facilitates rapid enrollment into joint replacement studies.

Laparoscopic & Non-laparoscopic

Lotus Clinical Research has extensive experience both as a site and CRO in the following soft tissue surgical models:

- **Herniorrhaphy (open and laparoscopic)**
- **Hysterectomy (open and laparoscopic)**
- **Colon surgery (open and laparoscopic)**
- **Bariatric surgery**
- **Laparoscopic cholecystectomy**

Abdominoplasty is generally a superior soft tissue model to all the model choices listed above. However, there are circumstances in which abdominoplasty is either not appropriate or not feasible. In these situations, Lotus Clinical Research recommends that sponsors explore one of the models listed above.

Lotus Clinical Research has implemented the following key success factors in previous soft tissue surgery trials:

- **Selection of sites with a history of reliable enrollment**
- **Consensus building among surgeons and anesthesiologists regarding an acceptable regimen of preoperative medications**
- **Standardization of ancillary hospital services that tend to confound analgesic results (physical therapy, nerve block, local anesthetic wound infiltration, and incentive spirometry)**
- **Subject training regarding differentiation of bloating and cramping (visceral discomfort) versus incisional pain (somatic discomfort)**
- **Placebo response training for study subjects and research staff**

Enrollment results

Lotus Clinical Research is located inside of Huntington Hospital, which is a large tertiary care center with a high volume of abdominal soft tissue surgeries. As such, Lotus Clinical Research has long standing relationships with multiple general surgeons and anesthesiologists within the hospital. This facilitates rapid enrollment into soft tissue surgical research studies.

Dental Pain & Third Molar Extraction

Of all the acute pain models one can choose from, dental pain has been shown to have the greatest assay sensitivity, fastest recruitment, and the lowest cost.

Lotus Clinical Research is an ideal choice for dental pain (third molar extraction) studies, not only due to our capabilities in the dental model itself, but also for our ability to advise and conduct later phase studies. Most sponsors who are involved with dental pain programs are planning their Phase IIb and Phase III programs. This planning process necessitates strategic decision making and regulatory correspondence. Having Lotus Clinical Research on board during this critical early period is of significant value.

For dental trials, Lotus Clinical Research provides both CRO and site services. We can perform single-center dental studies within our own walls, and also utilize a network of well-vetted sites throughout the country for multicenter investigations.

Minimizing Variability

The key to success in dental surgery is minimization of variability, which can be achieved by:

- **Ensuring that all sites appropriately identify impaction levels**
- **Utilizing a pre-specified impaction grading scale**
- **Homogenizing and adhering to a standard anesthetic regimen**
- **Placebo response training for subjects and staff members**

Subject Recruitment

With 17 million people in the greater Los Angeles area and proximity to six local colleges, recruitment into dental studies at the Lotus Clinical Research dental site is swift and reliable. Additionally, Los Angeles provides a diverse ethnic group, which is an important component of early phase research.

Our recruiting team consists of multiple full-time call center operators, a call center manager, and a media buyer. They achieve excellent results by utilizing our in-house database, social media, and newspaper/radio advertisements.

Dental Facilities

Lotus Clinical Research utilizes a board-certified, oral-maxillofacial surgeon to perform the extractions. The surgical suite is outfitted with state-of-the-art equipment, including a digital panoramic x-ray system (good visualization is critical for determining impaction level).

Enrollment

Average enrollment is 30+ subjects per month at the Lotus Clinical Research site. Screen failure rates average from 25-30% based on specific inclusion/exclusion criteria and dental x-rays.

Chronic Pain Models

Unparalleled research support for innovative chronic pain therapies.

From early phase proof of concept through Phase 3 studies, Lotus Clinical Research specializes in designing chronic pain models that address every aspect of chronic pain studies, resulting in greater efficiencies and superior outcomes for sponsors.

Chronic Low Back Pain

Chronic low back pain is a common analgesic model because of its high prevalence and clinical significance. Lotus Clinical Research has experience and proficiency in both neuropathic and non-neuropathic low back pain studies, and we have enrolled both opioid experienced and opioid naïve subjects into our clinical trials.

EERW Designs

Enriched Enrollment Randomized Withdrawal (EERW) designs are common in chronic pain investigations because they confer greater assay sensitivity. Appropriate implementation experiments with EERW designs can have logistical challenges. Lotus Clinical Research has the requisite knowledge and experience to successfully run EERW LBP studies.

Radicular Pain

Investigations into radicular low back pain (low back pain with a neuropathic component) can be difficult to implement. Lotus Clinical Research has initiated multiple studies in which we have executed intensive investigator training to standardize the diagnosis of radicular low back pain. We have a network of sites that are experienced in quantitative sensory testing with neurologists on staff serving as either principal or sub-investigators.

Imaging (CT and MRI)

Lotus Clinical Research has close relationships with imaging centers near its research unit. We have utilized both CT scans and MRI scans for various low back pain investigations. Our trained investigators can inject investigational product under fluoroscopy with retention of the video images for future use.

Opioid-Induced Constipation

Lotus Clinical Research has successfully completed multiple OIC investigations both as a research site and as a CRO. We are recognized nationally for our work in OIC

Because of our extensive experience, Lotus Clinical Research has the ability to advise its clients on issues that will be critical to the success of any OIC investigations, including:

- **Expected run-in failure rate based on study specific inclusion/exclusion criteria**
- **Techniques to improve subject diary compliance**
- **Subject training to improve reporting consistency around Spontaneous Bowel Movements (SBMs)**
- **Subject training on the Bristol stool scale**
- **Methods to rate/adjudicate CNS adverse events**

Clinical Opioid Withdrawal Scale (COWS)

Lotus Clinical Research has developed a proprietary training tool for study investigators around the proper performance of the COWS. The system involves video training and several post-training vignettes. Test results are scored and retained in the study site regulatory binder.

Database

Lotus Clinical Research has the nation's largest OIC database consisting of over 12,000 study volunteers with chronic pain. The database is mature, well maintained, and sortable for criteria specific to OIC studies, such as: total daily morphine mEq intake, historical weekly bowel movement frequency, and pain etiology.

CNS & Gastrointestinal Adverse Event Adjudication

Properly evaluating central and gastrointestinal withdrawal symptoms requires not only training but also a significant amount of experience. At Lotus Clinical Research, we have enrolled hundreds of patients into OIC trials, which ensures our physicians, allied health professionals, and study coordinators have the requisite knowledge to accurately evaluate and adjudicate OIC related adverse events.

Gastrointestinal withdrawal symptoms can range from mild and tolerable to severe and disabling. In many early phase protocols, severe GI symptoms are an MTD criteria, making appropriate assessment of GI AEs even more critical. CNS withdrawal is a safety concern for any opioid antagonist. Beyond understanding how to conduct COWs and SOWs questionnaires, the site must also ensure that the patient has adequate opioid reserves so their baseline opioid intake is not disrupted. These disruptions can lead to inadvertent withdrawal not related to the study medication, which can confound study results.

Enrollment Results

PHASE	SPONSOR	ENROLLMENT PERIOD (MONTHS)	ENROLLED BY LOTUS	TOTAL STUDY N	COMMENTS	CLINICAL TRIALS GOV ID.
2	Alkermes	7	14	60	Top Enroller	NCT01100151
3	Progenics/ Salix	5	39	700	Top Enroller	NCT01186770
1	Adolor	3	22	22	Single Site, Multiday Confinement	Not Available (Phase 1)
2a	Adolor	6	77	120	Top Enroller	NCT01207427
1	Adolor	2	24	24	Single Site	Not Available (Phase 1)
1/2	Theravance	2	29	70	Top Enroller	NCT01040637
1	Adolor	1	7	24	*Rescue Site	Not Available (Phase 1)

Osteoarthritis

Lotus Clinical Research has performed multiple osteoarthritis investigations as both a research site and as a CRO. We are experienced in the osteoarthritis flare model within subject crossover designs and parallel group designs.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is an endpoint that is commonly used for osteoarthritis studies. Unfortunately, a common problem encountered when using the scale is that it is not always well understood by research personnel and/or study subjects.

In order to help remedy this issue, Lotus Clinical Research has developed a proprietary osteoarthritis training toolkit. This package has been successfully deployed in both single and multicenter osteoarthritis investigations over the past several years.

Lotus Clinical Research's Osteoarthritis Training Toolkit

Our Osteoarthritis Training Toolkit provides study subject education via video training on using common osteoarthritis questionnaires effectively, avoiding placebo response, and the proper use of rescue medication.

In addition, our toolkit provides investigator and key study staff training focusing on appropriate study conduct. Specific issues that are addressed include:

- **Avoiding bias in participant communication, helping patients use osteoarthritis questionnaires correctly, minimizing placebo response, and providing proper instruction to study subjects on the use of rescue medication.**
- **Increases data uniformity within and across the study sites.**
- **Maximizes accuracy and precision in osteoarthritis questionnaire responses.**

Enrollment results

Average enrollment is 15 subjects per month at the Lotus Clinical Research site. Screen failure rates average 20-25 percent based on specific inclusion/exclusion criteria and may be slightly higher if a washout period is required for randomization.

Early Phase

Phase 1 and Analgesic Proof-of-Concept

Lotus Clinical Research's patient training tools and data collection methodologies result in reduced variability and improved statistical sensitivity toward the primary efficacy endpoint.

Multi-Day Confinement, Pharmacokinetic and CSF Collection

Lotus Clinical Research has the ability to house analgesic and surgical patients for up to 30 days in order to:

- Collect pharmacokinetic and CSF samples
- Control study confounders and monitor diary data
- Ensure medication compliance
- Maintain strictly regimented diet plans
- Closely observe for safety

Located Within A 675-Bed Multispecialty Community Hospital

Lotus Clinical Research operates a 40-bed phase 1 unit located within a community hospital, providing our clients with unprecedented access to medical subspecialists and technological resources. The emergency room is 100 yards away and the hospital code team will respond to our unit conferring an additional layer of safety to our subjects.

Contracts Independently and Utilizes Central IRB

Although Lotus Clinical Research is located inside a hospital, it is an independent business unit which means that it can utilize a central IRB and execute contracts independently from the hospital. This results in rapid study starts that are not tied to the institutional bureaucracy typical of other hospital-based units.

Contemporaneous Pharmacokinetic/Pharmacodynamic Assessments

The Lotus Clinical Research phase 1 team is skilled in pharmacokinetic assessment and processing. All staff who handle blood products are IATA certified. The unit is equipped with a refrigerated centrifuge and minus 70-degree freezer.

Double Stopwatch Technique

Our staff has extensive experience with the double stopwatch methodology. Subjects are trained with our proprietary tools to understand the difference between perceptible and meaningful relief.

Topical Hemostasis

We are a leader in hemostatic investigations enrollment and topical hemostat study execution.

Lotus Clinical Research has a vast amount of experience in performing trials on topical hemostats and has been integrally involved with the following programs: Grifols (topical human thrombin), Zymogenetics (recombinant human thrombin), King Pharmaceuticals (bovine thrombin), and Profibrix (fibrocaps spray thrombin).

We are well published in the field of topical hemostats and have been the highest enrolling site in nearly every one of our hemostatic investigations. We are facile at performing Time to Hemostasis (TTH) measurements and have developed proprietary TTH measurements between study centers.

Time to Hemostasis Measurements

While TTH measurements may appear to be straightforward at first, they actually require a significant amount of experience to standardize and accurately capture.

At Lotus Clinical Research, we have performed over 500 TTH measurements in various hemostatic models including:

- **Spine surgery (epidural bleeding)**
- **Vascular surgery (anastomotic bleeding)**
- **Soft tissue surgery (diffuse venous ooze)**
- **Laparoscopic surgery (parenchymal bleeding)**

Through this experience, we have learned several nuances that help us select appropriate bleeding sites, follow detailed TTH protocols, and accurately determine when hemostasis has been achieved. Additionally, we are skilled at identifying rebleeds per the strict definition of the study protocol.

Proprietary High Volume Low Variability Hemostasis Models

Lotus Clinical Research has developed two proprietary surgical hemostatic models, mastopexy and abdominoplasty, that can be integrated into early or late phase clinical trials on surgical bleeding.

These models have several advantages over classic bleeding models such as spine surgery and vascular surgery, including:

- **Variability reduction due to:**
 - (1) multiple potential bleeding areas to be utilized as hemostatic targets so that the surgeon can pick uniform sites among the full cohort of subjects, reducing inter-subject variability;
 - (2) single surgeon performing all operations therefore improving intra-rater reliability.
 - **Low intraoperative screen fail rate (=5%).**
 - **Standard of care does not involve anticoagulation for these subjects.**
 - **Patients involved in these models are generally healthy with few adverse events which leads to less confounding of the investigational product's true adverse event profile.**
 - **High-volume recruitment per site improves timelines and provides significant cost efficiencies secondary to decreased monitoring and start up expenditures.**
-

Enrollment Results

A large analgesic clinical trial database with over 58,000 potential study volunteers.

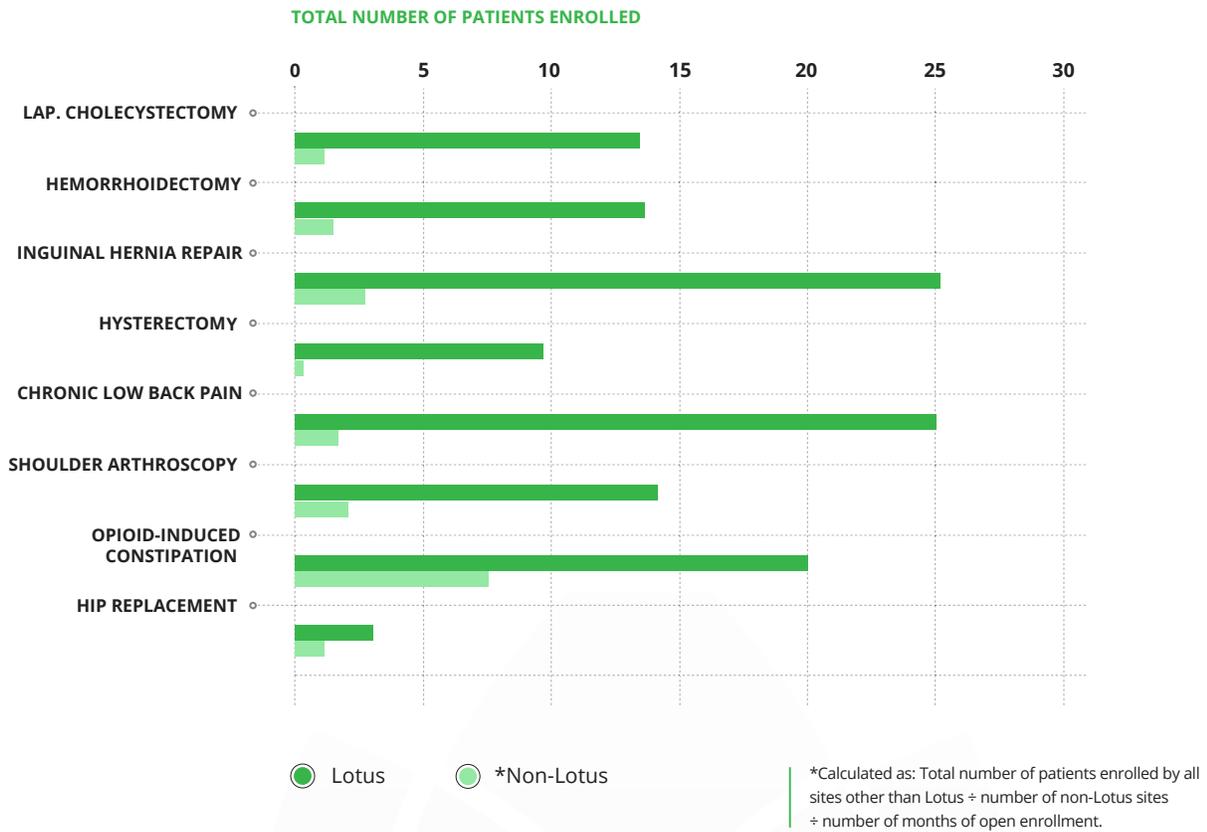
Lotus Clinical Research is renowned as a top enrolling center for all types of analgesic research studies. We have a large analgesic clinical trial database with over 58,000 potential study volunteers. Our database has been accrued since 2001, utilizing over \$5 million dollars in cumulative advertising funds.

The database is sortable by multiple factors, including specific analgesic disease state (low back pain vs. neuropathic pain, etc.) and daily morphine mEq consumption. It is actively maintained, sorted, and pruned to yield excellent enrollment results.

PHASE	CONVENTIONAL SURGICAL MODEL	LOTUS RECRUITED SURGICAL MODEL
Recruitment Strategy	Accrual from existing practice and surgery calendar... “watch and wait” for patients	Active recruitment using television, radio, newspaper advertisements and social media as well as surgery calendar
Ethics Review	Local IRB (4 - 8 weeks)	Central IRB (2 - 4 weeks)
Standardization	Hindered by large healthcare team involved in hospital based patient care	Optimized secondary to research team providing all care: surgeon, anesthesiologist, and nurses are all part of the study team
Cost	Increased secondary to need for multiple centers and high degree of coordination on behalf of the CRO	Decreased secondary to high volume patient throughput. Project costs can be reduced by over 30% compared to a larger, multicenter trial as a result of reduced time for investigator recruitment and training, CRA travel, project management, etc.

Analgesic Expertise

PHASE	PLAIN MODEL	PTS PER MONTH LOTUS SITE	PTS PER MONTH NON LOTUS SITE	CLINICAL TRIALS GOV ID.
3	Lap. Cholecystectomy	13.3	1.1	NTC01052012
3	Hemorrhoidectomy	13.5	2	NTC00744848
3	Inguinal Hernia Repair	25.2	3.2	NCT00551135
3	Hysterectomy	9.2	0.4	NTC00468845
2	Chronic Low Back Pain	25	10	Link Not Available
2a	Shoulder Arthroscopy	13.8	2.9	NTC00811577
2a	Opioid-Induced Constipation	20	7	NCT01207427
3	Hip Replacement	3.3	1.2	Link Not Available



Key Personnel

Meet the medical and scientific experts who make Lotus Clinical Research a leader in analgesic studies.



Sonia Kaur, DO

Medical Director

Dr. Sonia Kaur is a board-certified physician with over 16 years of experience in analgesic research. She has served as the medical monitor, principal investigator, or sub investigator on over 200 pain studies. In her current capacity, Dr. Kaur provides medical oversight of the Lotus Clinical Research investigative team to ensure proper study conduct and optimal patient safety, and is responsible for liaising with the sponsor's chief medical officer.

She spearheads Lotus Clinical Research's internal placebo response staff education training program. From 2008-2011, Dr. Kaur served as the chairman of the Glendale Adventist Hospital IRB.



Anne Arriaga

Chief Operating Officer

Anne Arriaga joined Lotus in 2008 and has since assembled a top-quality team of investigators, project managers, and study coordinators. She has managed the clinical operations and execution of over 500 trials, of which over 300 were analgesic trials.

She has a bachelor's degree in healthcare administration, a degree in nursing, and post-graduate training in clinical research management and project management. Prior to joining Lotus, Mrs. Arriaga served for 10 years as the Vice President of Clinical Operations for a 120-bed Phase 1 unit.



Eric Guitard, PMP

Director, Systems Integration

Eric Guitard is responsible for managing the experienced data management team. For seven years prior to joining Lotus Clinical Research, he managed the internal CRO functionalities of a biomedical company specializing in pain management. Mr. Guitard was responsible for all project management, data management, vendor management, and clinical program development. He holds a bachelor's degree in business administration from the University of Montreal and is also a Certified Project Professional Manager from the Project Management Institute.



Christopher Bowman

Director, Quality Operations

Christopher Bowman has over 19 years of experience in clinical research spanning regulatory compliance, quality assurance, and clinical management of Phase I through Phase IV studies. Prior to joining Lotus, he held positions as the Director of Clinical Operations for a clinical and regulatory consulting firm and served as the Director of Quality Operations for a large Phase I-IV clinical trial center. Mr. Bowman has extensive knowledge in Federal Regulations and GCP/ICH guidance with over 14 years conducting GCP compliance audits including investigational sites, sponsors, CROs, clinical vendors, trial master files, IRBs, and FDA readiness visits both in the U.S. and abroad.



Jennifer Nezza

Director, Biometrics

Jennifer Nezza is responsible for the management of biostatistics team, providing technical leadership on the biostatistical aspects of numerous development projects in North America, as well as, serving as lead statistician on multiple global programs. Prior to joining Lotus, she served as a senior biostatistician for a bio/science company for eight years and was a member of the biostatistics leadership team of a global CRO for more than 10 years. Jennifer has supervised the statistical aspects of Phase I through IV clinical trials from design through analysis and reporting for both traditional and adaptive study designs in a broad range of therapeutic areas including analgesia. Jennifer has represented the biostatistics department with interactions with sponsor companies, in multiple NDA submissions, including developing ISS/ISE and eCTD submission ready documents, and represented multiple sponsors in both phone and face-to-face interactions with regulatory agencies including the FDA. She is a member of the American Statistical Association and holds BA and MS degrees in statistics.

Analgesic Approvals

Our clients include the most recognized and respected pharmaceutical companies in the U.S. and around the world.



Dr. Singla helped design, plan, and execute the Xartemis Phase II and Phase III programs. He contributed to the program by serving as: a regulatory consultant, principal investigator, and the lead author on both the CSR and pivotal efficacy publications. Dr. Singla is also involved with the post marketing team at Mallinckrodt and has initiated an investigator sponsored study to garner more clinical data and experience with the molecule.



Lotus enrolled 174 patients undergoing major surgery (hip replacement, knee replacement or open abdominal surgery) in 12 months. The study had a total n of 900. An average non-Lotus site enrolled 25 patients.



Lotus enrolled 58 patients into Pacira's Phase 2 surgical hemorrhoidectomy study in 6 months. Seventeen non Lotus centers participated in this clinical program, each enrolling an average of less than 2 patients per month.



Lotus was a top enrolling site in the bunionectomy program. Lotus enrolled 156 patients over 5 months. The total n for the study was 602. The data was positive for the primary endpoint. The FDA considered this to be the sponsor's pivotal study and granted approval based on the data.

Analgesic Approvals



In order to support a 5-day labeling claim, Cadence needed to utilize the multi-day domiciling facilities of Lotus Clinical Research. After study subjects had major surgery in the hospital, they were transferred to Lotus on Day 2 and received study medication for an additional 3 days.



Instead of performing this 320 patient open abdominal surgical model at a multitude of US sites, Roxro chose to activate only 3 well known analgesic investigative sites of which Lotus was one. The endpoint was met and the drug received regulatory approval.



Lotus was involved in the pivotal registration study for IV Motrin. We were a lead enrolling site and Dr. Singla authored a key publication on this molecule which can be found on our website.



Lotus employed its recruited research model on several investigations involving Pregabaline. Dr. Singla worked closely with the scientific officers at Pfizer to evaluate the efficacy of Pregabaline in patients undergoing surgery in two acute pain models; open inguinal hernia and total abdominal hysterectomy. When comparing enrollment between Lotus and an average non-Lotus site, one finds that Lotus enrolled 10 times as many patients as an average site. Enrollment is not the end of the story. Not only were the enrollment metrics better, but also the effect size generated at Lotus was significantly greater than that generated at non-Lotus centers.



The 2 pivotal efficacy studies on DepoDur were the first set of investigations performed at Lotus in 2001. Lotus was the lead enrolling site in both studies.



Better Science. Superior Results.

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