



Excellence in CNS Clinical Trials

We work to find a better way. We work to raise standards and deliver more. We break new ground to make progress possible.

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ICON is a global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries. We specialize in the strategic development, management and analysis of programs that support Clinical Development - from compound selection to Phase I-IV clinical studies.

Prolonged life expectancy and an ageing population are likely to increase the prevalence of many chronic and progressive CNS disorders. It is predicted that by 2020 the proportionate share of global burden of neuropsychiatric disorders will have risen to 14.7%⁽¹⁾.

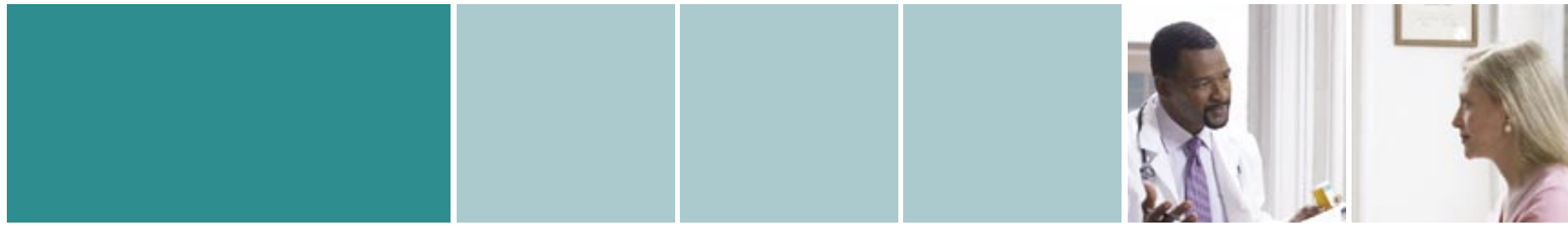
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The demand for CNS drugs is expanding due to improved understanding of the underlying neuropharmacological mechanisms in the general practice community and patients. CNS drugs form a significant part of the overall pharmaceutical market and represent 20% of all new compounds entering clinical trial testing. It is one of the most rapidly growing areas of medical and pharmaceutical research, a trend that is expected to continue over the next decade with predicted sales growing to US\$68 billion by 2009⁽²⁾.

Reference

(1) Global Burden of Disease Report

(2) Bio/Pharmaceutical R&D Sourcebook 2006/2007



Challenges and Solutions

CNS Drugs: The Opportunity

Despite the tremendous increase in CNS knowledge in recent years, the pathophysiology and pathogenesis of most CNS disorders is still poorly understood:

- There are significant unmet therapeutic needs for psychiatric and neurological diseases, in terms of both efficacy and safety, since the majority of disorders are chronic in nature and most existing treatments are only symptomatic, not curative
- Existing drugs show a low patient response rate of only 40–60%
- Response prediction for individual patients is poor and usually only possible based on patients' previous response to similar drugs
- The safety profile of many CNS drugs is not ideal due to marked side effects

This all translates to market opportunity for sponsors but not without significant, specific challenges.

Patient Recruitment

Because of the diversity in CNS disorders, patient recruitment challenges often vary according to the disorder. For example, in Alzheimer's and the Psychotic disorders, the process of obtaining informed consent is more complicated because, in addition to the patient giving consent, the caregiver must also assent to the patient's participation. In the case of depression, many patients can be reluctant to consult a psychiatrist, preferring to seek help through their General Practitioner, so anti-depressant trial recruitment may be more effective through patient directed approaches.

ICON's knowledgeable and experienced staff can advise you on key elements that will help meet your patient recruitment and retention targets. We have strategically located offices for optimal patient recruitment, whatever the challenge.

Expertise and Support

CNS Therapeutic Aligned Group (TAG)

ICON's CNS TAG is comprised of international therapeutic specialists who are experienced in clinical research and drug development. They provide strategic knowledge and expertise in the development of CNS drugs and are involved in all stages of the study:

- Project feasibility
- Protocol development, review and evaluation
- Clinical trial planning
- Selection of investigator sites
- Therapeutic training and advice
- Project oversight
- Consulting, medical monitoring and advisory board representation
- Interpretation of the clinical data

Diagnostic procedures, clinical trial methodology and assessment methods in CNS drug development differ in many respects from those

in other therapeutic areas. ICON's CNS TAG can provide the specialist knowledge that is required to ensure these factors are taken into account and can provide insight into:

- CNS diseases – diagnosis and treatment
- Currently available CNS drugs – mode of action, efficacy, safety
- Specific risks of CNS drug development and their management
- Specialized knowledge of clinical trial methodology and efficacy assessment methods
- Access to and relationships with Key Opinion Leaders and CNS Investigators in various regions of the world

We also have a team of Clinical Project Managers and Clinical Research Associates with experience in all major CNS drug classes across all key areas of CNS drug development.

Excellence through Experience

Our experts have conducted over 450 studies representing 69,000 patients and 6,900 sites, across the globe over the past 5 years.

ICON has extensive experience in global clinical trial management including a wide range of CNS agents. These trials have consistently been completed on or ahead of schedule and within budget. Our clients know they can rely on us for flexibility, efficiency and unsurpassed quality.

Capabilities in CNS include:

- Development, advisory and regulatory services
- Phase I clinical pharmacology services including unique CNS pharmacodynamic models
- Full service Phase II-IV clinical trial management
- Extensive testing facilities at central laboratories that are ISO 17025 certified
- Medical imaging services with strong experience in CNS trials
- Customized Interactive Response Systems (IVRS) and Interactive Web Response Systems (IWRS)

Case Study:

Placebo controlled phase III clinical trial in patients with Huntington's Disease.

Number of patients: 240

Territory: Europe

Key Challenges & ICON Solution:

Approval process in certain countries

ICON worked closely with the client to revize timelines due to delays in the regulatory approval process. A steering committee was set up to oversee the smooth implementation of revized targets and regular meetings were held to review the study status.

Patient recruitment due to low incidence of Huntington's Disease

Relationships were established with patient self-help groups as a means of advertising. The Huntington's Disease network, an association of specialist research, proved invaluable in meeting recruitment targets.

Investigator site resources

Lack of motivation was an issue at some sites due to shortage of resources. A physician strike during the trial also presented a challenge where patients could only be recruited every other week. ICON increased the number of monitoring visits to the affected sites and additional resources (e.g. study nurse) were offered to support coordination.

Outcome:

The study was completed on schedule and all patient recruitment targets were successfully reached.

Case Study:

Clinical trial to compare the safety and efficacy of two clinical compounds in treatment naïve patients with RRMS who had recent Multiple Sclerosis (MS) disease activity as demonstrated by clinical relapses.

Number of patients: 1500

Number of sites: 95

Territory: 2 countries

Key Challenges & ICON Solution:

Lack of consistent imaging, imaging timepoints and lack of quality across sites.

ICON Medical Imaging conducted site technical evaluations and site training to ensure image quality thus reducing the turn around time and expediting the clinical process.

Outcome:

The study is ongoing and continues to remain on schedule.

ICON's Central Laboratories has performed over 4 million tests on 608,628 samples received involving more than 45,000 patients in CNS studies.

ICON's CNS Trial Experience over the past 5 years

	No. Trials	Phase	Regions	Patients	Sites
ADHD & ADD	7	Consulting, I, II, III and IV	Eastern Europe, North America, Western Europe	701	170
Anxiety Disorders	24	Consulting, I, II, and III	Asia, Eastern Europe, Latin America, North America, Western Europe	3613	365
Alzheimer's Disease	32	Consulting, I, II, III and IV	Australia, Asia, Eastern Europe, Western Europe, North America, South Africa	5148	531
Bipolar Disorders	13	Consulting, III and IV	Eastern Europe, Latin America, North America	2655	287
Cognitive and Attention Disorder	3	I, II and IV	North America	2300	110
Dementia and Neurodegenerative Disorder	6	Consulting, I, II and III	North America, Western Europe	990	125
Depression	28	Consulting, I and III	Asia, Eastern Europe, Latin America, North America, Western Europe	8645	563
Diabetic Neuropathy	11	Consulting, I, II and III	North America, Western Europe	3503	219
Epilepsy	34	Consulting, I, II, III and IV	Eastern Europe, North America, South America, Western Europe	1748	498
Migraine	18	Consulting, I, II, III and IV	Eastern Europe, North America, Western Europe	7230	936
Multiple Sclerosis	20	Consulting, I, II, III and IV	Eastern Europe, North America, South America, Western Europe	3090	340
Neuropathy	3	II	Asia, North America, Western Europe	95	30
Obsessive and Compulsive Disorder	1	Consulting		0	0
Panic Disorder	1	III	Australia, Belgium, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Portugal, South Africa	796	103
Parkinson's Disease	24	Consulting, I, II, III and IV	Asia, Eastern Europe, North America, South America, Western Europe	5222	569
Post Operative Analgesia	16	Consulting, I, II and III	New Zealand, North America, Western Europe	2415	55
Postherpetic Neuralgia	7	II and III	North America, Western Europe	810	257
Schizophrenia	23	Consulting, I, II, III and IV	Asia, Eastern Europe, North America, Western Europe	3189	376
Smoking Cessation	8	Consulting, II, III	Australia, North America, Western Europe	6944	108
Sleep Disorders	34	Consulting, I, II, III and IV	Australia, Eastern Europe, North America, Western Europe	4992	843
Substance Use Disorder	11	Consulting, I, III and IV	North America, Western Europe	884	74
Traumatic Brain Injury	2	Consulting, III	North America, Western Europe	148	47
Pain	125	Consulting, I, II, III and IV	Australia, Western Europe, North America, South America	4542	321
Vascular Dementia & Neurodegenerative Disorder	7	II and III	Asia, North America	84	7
Totals	458			69,744	6,934

Table correct as of May 2007

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