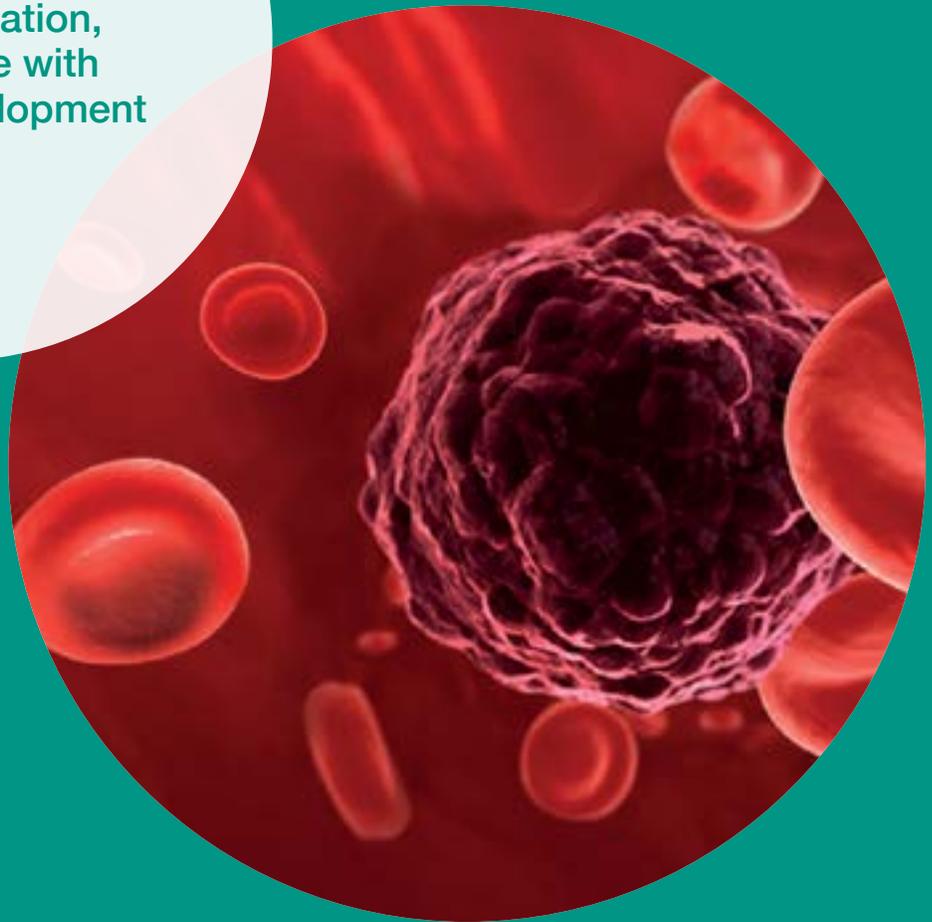


# Oncology Clinical Trials

From early phase to  
commercialisation,  
we accelerate with  
smarter development



## The rising complexity of oncology

The success of any oncology clinical trial relies on sound science, therapeutic expertise, global field experience and a fully integrated plan that both anticipates the pitfalls of the development lifecycle and prevents them from derailing the compound — or the futures of other good drugs in a portfolio.

For the last 25 years, ICON has met the challenges posed by increased trial complexity and mounting regulatory and reimbursement hurdles with some of the most important clinical insights and innovations.

ICON experts lead clinical trials with the most innovative technologies in the industry at their disposal, including tools developed at ICON for adaptive trial design and execution, investigator training, medical imaging, an improved error-based approach to risk-based monitoring, and real-time data integration. Our Firecrest platform is a web-based platform that is not only a market leader in training but offers eConsent and patient portal functionality.

From strategic development to programme management, data analysis to commercial guidance, each of the ICON service areas of expertise are led by today's foremost innovators and problem solvers in clinical development.

In the past 5 years alone ICON has been engaged in over 300 early phase and registration oncology studies, providing a range of integrated services:

- Development
- Consultancy
- Clinical Operations
- Data Management
- Statistics
- Medical Imaging
- Laboratories
- Peri-approval
- Pricing and Market Access
- Medical Communication
- Technology Solutions

We have touched the lives of almost 40,000 oncology patients across 11,000 sites and 23 countries. With established relationships in oncology centres, including a strong network of Key Opinion Leaders globally, ICON is the partner of choice for those seeking the competitive advantage needed to succeed in today's global drug development landscape.

Oncology Experience Project Management / Monitoring - Past 5 Years			
Phase	No. of Studies	No. of Patients	No. of Sites
I	102	2685	714
II	114	8297	2750
III	67	20016	6758
IIIb	4	1159	314
IV	17	5203	916
Not Classified	1	91	47
<b>Clinical Total</b>	<b>305</b>	<b>37451</b>	<b>11499</b>



Of our current oncology portfolio is focused on Immuno-oncology. Multiple studies including anti-PD-1, PD-L1, CTLA-4 and OX40 amongst other trial molecules as single or combined agents.



Percentage of our current work is in the hem-onc space.



Of our studies are early phase trials from first time in man, to proof of concept, to dose finding studies.

**Genomics England**  
ICON is helping to support better diagnosis and better treatments for patients with cancer and rare diseases through the 100,000 Genomes Project. ICON was selected by Genomics England to help build the world's largest genome sequencing project:

- Data Management partnership
- Cleansing and validating data from over:

**70,000**   
patients   
and their families

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## Expert insight to accelerate your success

### Consulting

The Consulting Services Team enhances your competitive advantage by combining scientific leadership with therapeutic insight, expertise and creativity to validate your decisions and strategically solve your problems related to preclinical and clinical development, regulatory assessment, diagnostics, chemical manufacturing and controls and business process improvement.

### Biomarkers and companion diagnostics

ICON is a leader in addressing U.S. FDA and European IVD Directive regulatory and clinical trial requirements for in vitro diagnostic devices. We have powered more than 120 IVD projects, including genetic markers for detection of lung, colorectal and bladder cancers; immunoassays for detection of tumour-associated antigens; and companion diagnostics for indications such as colorectal cancer.

### Biosimilars Insight and support at every stage of the process

Biosimilars are relatively new to certain markets therefore sponsors need a partner who can provide an end to end solution with the insight to navigate an evolving regulatory environment and the unique operational challenges. ICON provides a fully integrated approach with strategic consulting to define the optimal development and commercial plans coupled with the operational capabilities to deliver optimal results. Specialist consultants will be with you at every stage of the process; from the selection of the target biologic, the characterisation of the structure, function of the molecule and process scale-up, phase I-III trial management right through to commercialisation.

### Comprehensive biostatistics experience

ICON's global biostatistics team provides services for clinical development plans, study design, statistical analyses and regulatory support.

In the past 5 years, our global team has supported over 500 trials—including 40 studies involving Drug Safety Monitoring Boards—and has generated over 124 CDISC-compliant (SDTM) datasets.

### Medical Imaging

For more than 20 years, ICON Medical Imaging senior personnel have assisted sponsors in hundreds of clinical trials for over 145 clients, resulting in more than 25 NDA/BLA submissions for regulatory approval. Senior ICON Medical Imaging experts have pioneered and continue to create methods, procedures and regulatory guidance that evolve today's standards. Our staff includes scientists who founded the first medical imaging core lab and experts who invented statistical criteria to assess reader performance.

### Medical Imaging services include:

- Efficacy and/or safety endpoints
- Full-service solution for diagnostic contrast agents and imaging device trials
- Electronic solutions for safety, endpoint and adjudication committees

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## MIRA™

ICON's MIRA technology provides complete access to all study data and complete visibility into your study's progress. MIRA protects against the risk of readers misinterpreting endpoints—an often-overlooked source of trial variability. MIRA is core to many companies' clinical data pipelines, including large pharmaceutical companies that have adopted the technology as a central repository for medical images.

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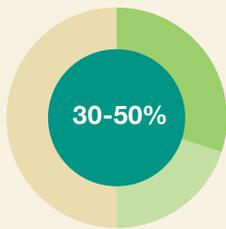
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## Leading the way in adaptive trial design and execution

According to the Tufts CSDD, 20% of clinical trials in 2013 used an adaptive design. Use of adaptive design has rapidly risen as sponsors capitalise on its ability to increase portfolio valuation by protecting good drugs from failure and improved decision-making at critical junctures in the development process.

### Adaptive Design Trials

For oncology trials, adaptive designs conserve patients and provide a more assured path to first-round success. ICON offers highly experienced professionals, market leading software, and a global footprint to make fully functional adaptive trials a reality.



Adaptive Designs have the potential to save between 30-50% on trial costs.

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## ADDPLAN

### Software suite for adaptive trials

ICON is the only CRO to offer a validated design, simulation and analysis software platform for adaptive clinical trials.

ADDPLAN® is currently licensed by regulatory agencies, including the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA).

ADDPLAN is also used by leading pharmaceutical and medical device companies and numerous academic researchers. It is the first statistical software package to incorporate a majority of the requirements detailed by the FDA in its draft guidance on adaptive design.

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### Always innovating

Oncology clinical trials are increasingly challenging. The need to screen multiple drug combinations for each cancer type has to be balanced against sponsors competing for resources i.e. patients and research sites.

Innovative approaches to trial design mean that the number of trials can be reduced without compromising data quality. ICON is actively implementing such strategies in the design and execution of immunotherapy programmes. ICON initiatives support our customers to achieve better and faster development of oncology drugs.

Further driving innovation is ICON's ADDPLAN DF Consortium, in which experts from leading pharmaceutical companies and ICON convene to enhance ADDPLAN with capabilities for the latest and most advanced adaptive trial methodologies.



15+

Years experience running Adaptive Clinical Trials



250

Adaptive projects in total



ICON's Innovation Centre provides methodology and execution expertise



1997: ICON's Hans Werner Voss conducts world's first Adaptive Clinical Trials - Asthma Study

## Combining optimised processes with advanced technology

### ICONIK

The ICONIK Informatics Hub is ICON's technology platform to analyse the operational, clinical and real world data that we collect during clinical development. We combine industry leading technologies with best practice processes to deliver real impact in clinical development and provide value to our clients. ICONIK helps visualise data trends across sites in real-time in a single holistic view, to improve data quality both in individual trials and across a portfolio.

Oncology-specific risk indicators can be built into your ICONIK platform to alert you to factors such as variability in tumour measurements or assessments obtained outside the protocol window, as well as trends in safety labs (LFTs, Blood counts etc) in close to real time. This can assist in reducing screen fail rates, observing differences in patient treatment variations by sites or country.

#### Proactive Risk Detection and Mitigation

Patient Centric Monitoring is ICON's risk based patient focused methodology for the design and execution of an adaptive monitoring strategy. It is already compliant with the risk based approach advocated in the 2016 update to ICH GCP guidelines.

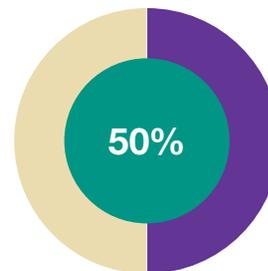
Patient Centric Monitoring incorporates a risk mitigation methodology known as Human Factor Analysis (HFA). ICONIK is used to systematically classify and analyse the causes of trial errors to help CRAs deploy the right risk-mitigation resources to the sites that need them most.

### FIRECREST

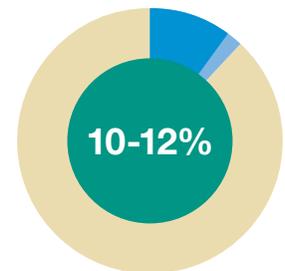
FIRECREST is a multi-award winning web based suite of digital products designed to enhance patient engagement and support investigators, patient recruitment and retention.

Delivering benefits from study start up to closeout, clients can use FIRECREST as their enterprise portal solution to manage their entire clinical development portfolio or on a study basis. The FIRECREST platform combines bedside data entry, electronic ICFs and a suite of award winning training modules relevant across multiple studies. It is deployed for more than 1000 studies with over 440,000 active users and comprises several solutions.

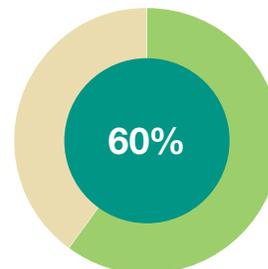
#### Firecrest has been shown to:



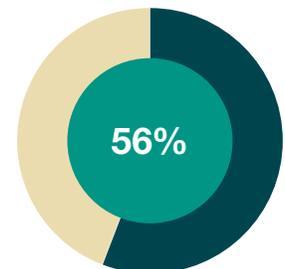
Reduce protocol deviations



Increase patient recruitment



Reduce mean training costs



Increase screening rates

From finding the sites with the most qualified investigators to employing risk-based monitoring to ensure quality control, ICON has the expertise and the tools to keep your trial on the right path.

### Enhanced study start-up performance

ICON applies a purpose-built advanced workflow software solution ACTIVATE that automates many study start-up activities, providing full visibility of the start-up process.

Country-specific workflows to guide study teams to complete the specific documents and tasks required for site activation, whilst tracking progress automatically. This level of transparency is of particular importance for oncology trials, where sub-committee approvals may be mandated and separate contracts with the different hospital departments are often required to be negotiated prior to site activation.

Together with our streamlined processes, ICON delivers study start-up performance of 3.5 month median cycle time from Protocol Approved to First Site Initiated - beating industry median by almost a month\*

# 3.5 months

median cycle time from Protocol Approved (PA) To First Site Initiated (FSI). Beating industry median of 4.2 months

### Data direct from Patients

Our dedicated Digital Services team can advise on harnessing new data sources from actigraphy and wearable devices, operationalising the collection, analysis and reporting of actigraphy data through ICONIK, our informatics technology platform.

ICON research, completed in association with Medidata and mProve Health, investigated industry perceptions towards a 'Bring Your Own Device' (BYOD) approach in clinical studies, enabling patients to use their own mobile devices to collect patient-reported outcomes (PRO) data.

BYOD has the potential to greatly enhance patient engagement and compliance. The research highlighted how commonly-cited concerns around proving equivalence across multiple devices are not as much of a deterrent to adoption as is often thought, boding well for the future of wearables in clinical trials, including remote monitoring.



\* Industry median 4.2 months according to KMR, a global leader in benchmarking, analytics and performance

## Better Data. Better Patients. Better Trials.

From finding the sites with the most qualified investigators to employing risk-based monitoring to ensure quality control, ICON has the expertise and the tools to keep your trial on the right path.

### Site selection and patient recruitment

For most trials, 20% of sites recruit 80% of patients. Some may not enrol a single patient. ICON project management teams and technologies find the sites and the patients you need to meet your deadlines. Partnerships with 1,200 key opinion leaders at world-class institutes and clinical networks mean your study will receive priority placement and expedited start-up.

### Real World Intelligence

ICON is enabling faster patient recruitment, and a reduction in the number of non-enrolling sites, through partnerships with a range of scalable web-based EMR interrogation platforms, which together provide real-world data sets representing 80 million patient lives.

### Global Site Relationships

ICON's acquisition of PMG Research provides sponsors with:

- An integrated network of clinical research sites that have the infrastructure at the site to manage the trial efficiently
- Strategically partnering with practices
- Unprecedented access via EMR
- Proven, highly skilled investigators
- Predictability and repeatability

ICON's integrated network of clinical research sites are also forging closer ties between industry and healthcare systems, and are providing patients with a valuable care option.

## IBM Watson

With around \$1.2 Billion spent on patient recruitment, 85% of patients unaware of clinical trials as a treatment option and as little as 3% of oncology patients participate in clinical trials. The current patient recruitment model is broken.

ICON and IBM are working together to revolutionise clinical trial feasibility, patient recruitment and study start-up timelines

- IBM Watson cognitive computing platform will be applied for Clinical Trial Matching Express to oncology clinical trials
- Identify exactly how many patients match trial criteria, where they are located and how to recruit them
- 25 oncology protocols
- Breast, Colorectal and Lung cancer indications
- Will enable real-time feasibility analyses, population modelling and trial protocol optimisation



## Proactive patient engagement and communication

When supporting oncology trial enrolment, ICON focuses on establishing a strong awareness campaign and establishing proactive site engagement activities.

The single most influential factor in enrolling patients in oncology trials is their physician. And while 84% of oncologists are reporting that they usually or always discuss clinical trial options with their patients, only 19% of patients report such a discussion. It is critical to improve the communications between the oncologist and the patient and establish trial awareness among patients, their families, the treating oncologists, and the study staff.

ICON's patient recruitment team ensures that stakeholders such as patients, families and the oncology community are aware of trials and how to participate at the local site level and online. Tools such as the Firecrest patient portal and printed material are used to educate patients and their loved ones on the trial to increase understanding and discussion with their oncologist. The team also proactively addresses any site engagement issues and ensures sites are successful by utilising a site engagement portal and clinical enrolment manager solutions.

## Clinical Enrolment Managers and their Impact on Oncology Trials

With the engagement challenges associated with oncology trials ICON has found that providing dedicated individuals to operationalise a protocol maximises site enrollment by utilising the Clinical Enrolment Manager (CEM) model.

Using a combination of calls and on site visits, the CEM focuses each oncology site on their customised recruitment strategy and providing assistance to them by:

- Translating protocol requirements into the sites' daily routine
- Developing site specific enrolment strategies based on local resourcing, site infra-structure and recruitment potential

- Reviewing and identifying gaps in site process for patient identification
- Assisting in the implementation of solutions to all identified enrolment gaps
- Identifying opportunities to strengthen existing and establish new referral networks
- Sharing enrolment best practices across sites



## Value-based healthcare and patient outcomes

ICON and the International Consortium for Health Outcomes Measurement (ICHOM) are partnering together to advance value-based healthcare by creating the world's first global healthcare outcomes benchmarking programme (GLOBE).

GLOBE aims to provide risk-adjusted, international benchmarks on health outcomes by medical condition.

Standard Sets provide a common language and approach to measuring targeted outcomes. By 2017, ICHOM expects to have published Standard Sets covering more than 50 percent of the global disease burden and currently has Standard Sets for the following malignant neoplasms:

- Colorectal cancer
- Breast cancer
- Localised Prostate Cancer
- Advanced Prostate Cancer
- Lung Cancer

ICON and ICHOM are measuring and reporting on outcomes that matter to patients, and are creating a platform to assess and compare outcomes from healthcare providers around the world. Together we are advancing value-based care by enabling the healthcare and clinical research industry to be more consistent, transparent, and patient-centric.

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## ICON laboratories and results management

### Central Laboratories

ICON Laboratories' extensive testing capabilities, combined with our clinical research experience and scientific expertise ensure that we can serve as a trusted partner for global oncology research programmes.

#### Oncology laboratory services include:

- Anatomic Pathology
- Biomarkers
- Molecular Pathology and Genomics
- Flow Cytometry
- Soluble Tumor Markers
- Sample Processing and Nucleic Acid Extraction
- Global Biorepository Services



#### Global Laboratory Footprint

Wholly-owned, independently operated network of laboratories in China, Singapore, Ireland and USA.



#### Therapeutic Experience

In the past 5 years alone, we have supported 500+ clinical trials in Phases I to IV, covering all major oncology indications.



#### Genomics

Collaborations with high-performance diagnostic providers including Cancer Genetics, Inc. and Empire Genomics.

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### Bioanalytical Laboratories

The bioanalytical laboratory services team provides support for both small and large molecule oncology therapeutics including development and validation of PK and anti-drug antibody assays.

#### In addition the group has:



supported sample analysis for 73 clinical protocols for oncology therapeutics in 2014



created ICON proprietary PK/ADA assays for 4 biosimilar oncology therapeutics



provided bioanalytical support for pivotal studies supporting the approval of an oncology biosimilar in Europe; currently supporting US trials for this biologic



provided bioanalytical support for 10 Antibody Drug Conjugate programmes over the last three years

#### Our Antibody Drug Conjugate programme offers:

- 5 assays offered to support a programme
- Antibody-toxin conjugate by ELISA (LBA group)
- Total Antibody by ELISA (LBA group)
- Unconjugated toxin by LC/MS/MS (MS group)
- Toxin + Linker (capability) by LC/MS/MS
- Immunogenicity (Anti-ADC antibodies) by ECLA (LBA group)
- In Q1 2015 55 clinical protocols for oncology therapeutics were supported

## From Clinical Development to Commercialisation

With the increasing need for evidence-based reimbursement decisions, it is more important than ever for sponsors to understand market demand and to share a robust and well researched health economic story for products in oncology, where reimbursement can be challenging.

ICON Commercialisation and Outcomes experts are engaged at the very beginning of a programme's design to ensure that the right data is generated to not only gain regulatory approval but to position products for the best reimbursement status in markets around the world.

ICON offers strong local market expertise and a global perspective to make sense of the multiple layers of healthcare systems around the world. We prevent market pressures and regulations from interrupting a clear commercial path.

### Services include:

- Peri-approval & Observational Research
- Global Pricing & Market Access
- Health Economics & Epidemiology
- Clinical Outcomes Assessment
- Healthcare Communications
- Language Services

A direct network of 1,000+ payer stakeholders and have access to additional specialists through our extensive range of global alliance partners.

Over the past five years, ICON has conducted over 400 oncology-related commercialisation projects in a variety of tumor types, from Phase 1 through post-launch and in all major US, EU, and emerging markets. Other notable experience includes over 60 HTA submissions, leading professional organisation task forces on rare & orphan drug development, and being chosen for collaborations by large government groups such as the FDA and FNIH.

The teams in-house healthcare communications team has completed over 150 oncology-related publication projects in the last year as well as a number of medical communications/medical affairs deliverables.

As novel oncology products come to market, ICON has developed effective value strategy platforms involving innovative evidence generation, modelling, and pricing methods to enhance quick adoption by reimbursement authorities and establish sustainable market positions over the lifecycle of a product.





**A Symbol of Excellence**

**Corporate Headquarters**

South County Business  
Park

Leopardstown

Dublin 18, Ireland

Tel: +353 (1) 291 2000

Fax: +353 (1) 291 2700

[Enquiries@ICONplc.com](mailto:Enquiries@ICONplc.com)

[ICONplc.com/oncology](http://ICONplc.com/oncology)