LUCID CONSULTING
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EU Clinical Trial Regulation

FROM LUCID CONSULTING

LUCID CONSULTING 2023

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EU CLINICAL TRIAL REGULATION
No. 536/2014 SPONSOR PREPAREDNESS

1. EU CLINICAL TRIAL REGULATION – SPONSOR PREPAREDNESS

How will my company be impacted by the EU Clinical Trial Regulation?

- The EU Clinical Trial Regulation No. 536/2014 will be implemented in January 2022 with the intention of making the European Union more attractive for clinical trials
- All interventional clinical trials in the EEA countries are in-scope (independent of the location of the Sponsor)
- Significant new operational, regulatory and compliance challenges

Centralized CTA process through the EMA portal (Minimal Viable Product)

Significant risks to multi-country approvals and clinical trial start-up times

New country level documentation requirements

New reporting requirements for Serious Breach of GCP

Risk of release of company confidential information

Complexity, financial and reputational risk: the General Data Protection Regulation

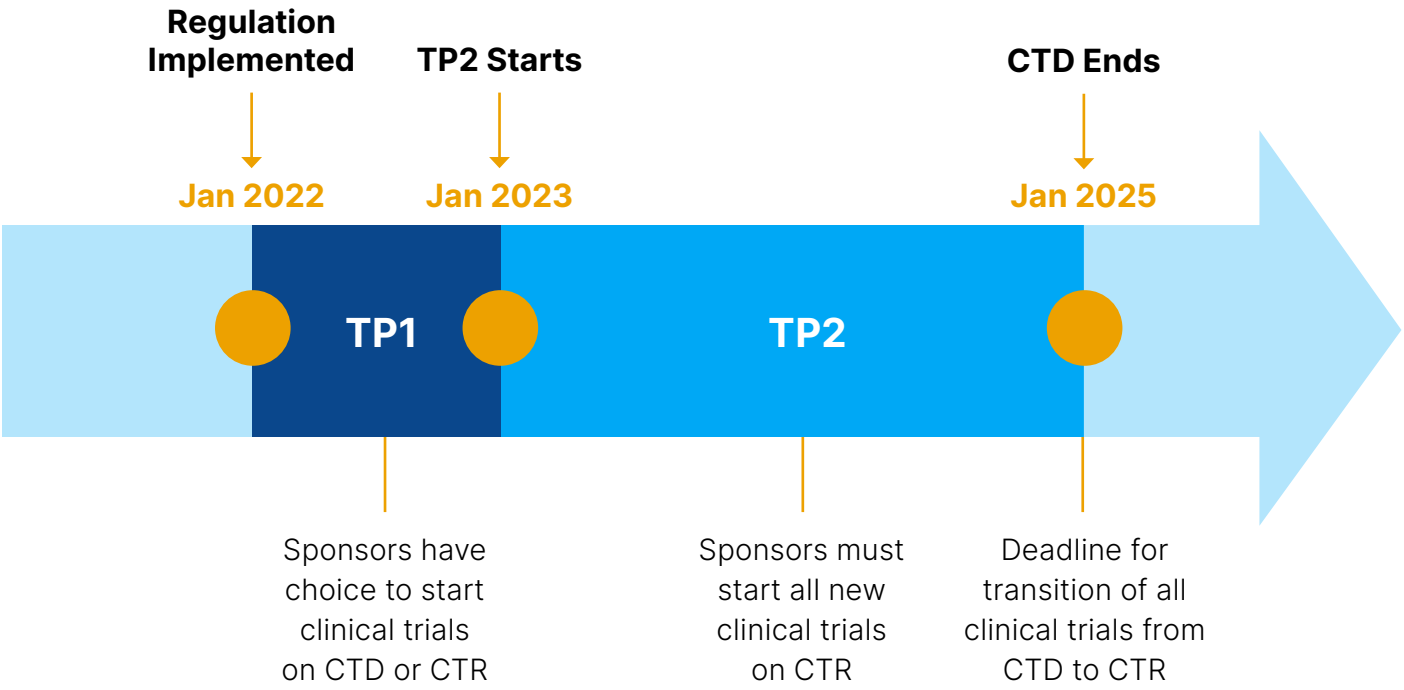
2 Quality Management Systems for 3 years

New, cross-company processes (Sponsor-CRO) need to be developed

Implementation challenges due to scale and scope of preparations

IMPLEMENTATION TIMELINES (REGULATION 536/2014)

Transition Periods



CLINICAL TRIAL APPLICATION

Practical Considerations and Logistics

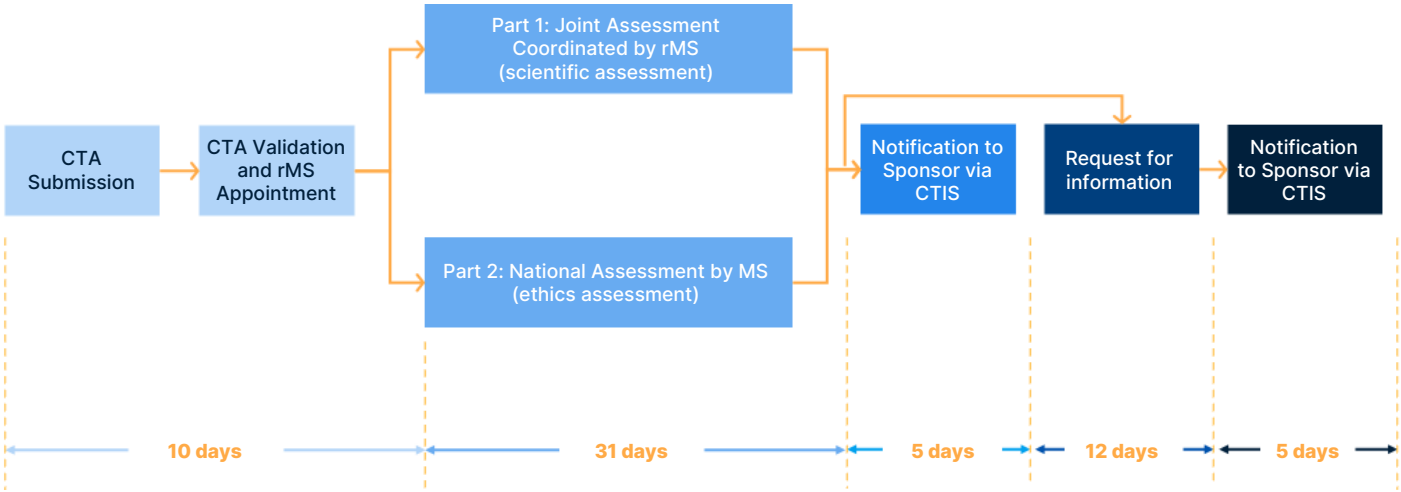
CTA Submission (or Modification)

1. Entire dossier needs to be submitted at once (Part 1 and Part 2 for all EEA countries involved in the clinical trial), although there is an option to submit Part 1 and Part 2 separately
2. All investigator sites need to be identified and included in the initial submission
3. Sponsor has the opportunity to request a rMS. However, the MSs will decide on the rMS
4. RFIs from MS will not be coordinated or rationalised by the rMS
5. Sponsors should be prepared that all information in the submission will available in the public domain (other than the quality section of the IMPD). Data protection and application of the GDPR is the responsibility of the Sponsor, not the EMA
6. CTIS only processes one active modification at a time

Notification Compliance

7. Significant number of compliance notifications are required throughout the lifespan of a clinical trial for each MS and EEA country. These most be submitted into CTIS within 15 days of the event including
   1) key milestones, 2) notification of halt/restart
   3) safety documentation e.g. DSUR
   4) serious breaches 5) inspection reports
   6) safety information

CLINICAL TRIAL APPLICATION
Submission Timelines in Calendar Days



Request for Information

- Request for Information (response to queries) will be a significant timeline challenge for Sponsor companies
- All responses must be submitted to CTIS within 12 calendar days of receipt. Unlike CTD, Sponsors must re-submit all updated documentation within the same timeframe

Failure to work within these timelines will result in a rejection and the need to re-start the process from the beginning

What does this mean in practice?

Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu
RFI Received			Public Holiday	1	2	3	4			5	RFI Response

- At certain times of the year, this equates to 6 working days
- Achievable if the request is simple e.g. editorial change

Knowing the culture and speed of decision-making in a Sponsor company (and in a CRO, if the clinical trial is outsourced); what is the likelihood that an RFI requesting a change to the protocol will be assessed, agreed to, updated and resubmitted in that timeframe?

CLINICAL TRIAL APPLICATION
Transitioning from CTD to CTR

All clinical trials run on the CTD framework must be completed by January 2025 or must transition to EU CTR

Important for Sponsors to take a strategic view of which trials should begin on CTD or CTR during Transition Period 1

Identification of long-duration clinical trials which will need to transition is important as transition from CTD to CTR is not likely to be simple

Administrative Transition

- A consolidated protocol without national amendments is a pre-requisite
- Clinical trial is ongoing
- No amendments ongoing under the CTD framework
- Administration documentation e.g. protocol, IB, upload plus placeholder documents for other documents required in CTIS

Full Transition

- Occurs when a first Substantial Modification is required
- All documents affected by the Substantial Modification must be uploaded, PPD removed and ready for publication
- The Substantial Modification blocks CTIS for between 60 and 106 days, so no other modifications can be submitted at this time

IMP and Labelling on Primary Packaging

- The Regulations outline multiple requirements relating to IMP and AMP, including Annex VI
- One of the most challenging for pharmaceutical companies who have invested in barcodes or QR codes may be the inclusion of expiry dates in number format
  - "Period of use (expiry date or re-test date as applicable), in month and year format and in a manner that avoids any ambiguity"
  - Vial size, primary packaging type, storage temperature maybe a challenge

CLINICAL TRIALS INFORMATION SYSTEM – EMA Portal for Clinical Trials

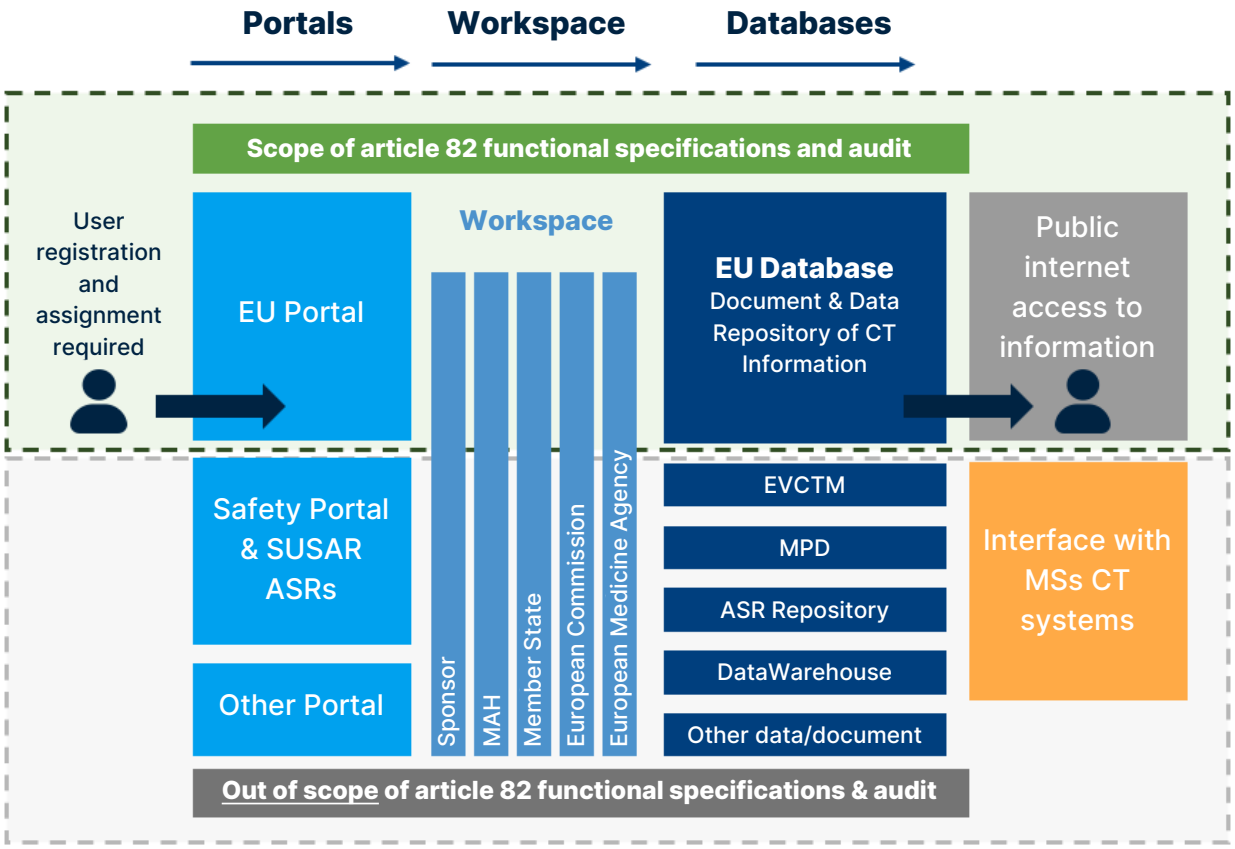


Figure 1. Schematic representation of the clinical trials information system (CTIS)

Clinical Trials Information System (CTIS): online modular training programme | European Medicines Agency (europa.eu)
Source: https://www.ema.europa.eu/

Protected Personal Data (PPD)

Sponsor is accountable for ensuring no Protected Personal Data is published by the EMA

All Part 1 and Part 2 must have PPD removed or redacted prior to submission into CTIS

- For documents where redaction is necessary, two documents will be submitted into CTIS

Examples of PPD can be found in many documents and include:

- Signatures
- Names
- Dates of Birth (for example, in Investigator CVs)
- Names of family (in Investigator CV)
- Unpublished references
- Consent for non-patient release of PPD obtained through contracts
- Identifiable information in Safety Narratives or Serious Breaches i.e. in small patient populations or small clinical trials (each Sponsor should take a legal review of what constitutes PPD)

Company Confidential Information (CCI)

- Excluding the quality section of the IMPD, it is considered that there is very little company confidential information within Clinical Trial Applications, although some Sponsors disagree
- Unlike Policy 0070, redaction of CCI is not allowed
- If a Sponsor believes the CTA submission contains CCI then the Sponsor should remove this from the application otherwise it will be published
- Sponsors have the option to defer publication based on strict rules. These deferrals may be overturned by a Freedom of Information Request

Phase	Maximum* Deferral
I	7 years
II, III	5 years
IV	0 years

* Maximum deferral is requested based on significant justifications. The EMA and MSs will not accept maximum deferrals on all clinical trials as this opposes the transparency agenda

Lay Language Summaries

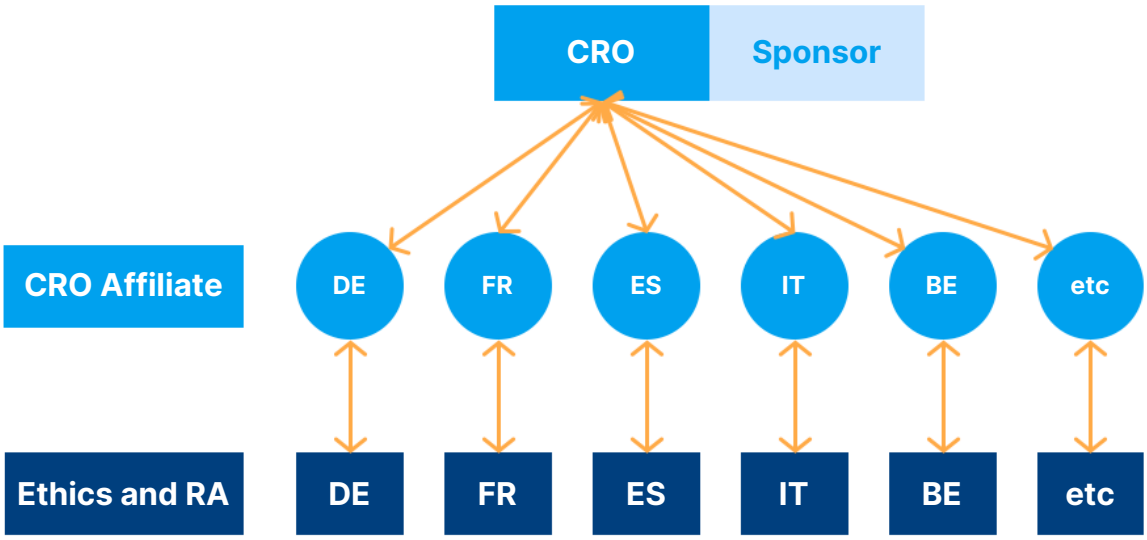
- Article 29.6 **The subject shall be informed that the summary of the results of the clinical trial and a summary presented in terms understandable to a layperson** will be made available in the EU database
- Details of requirements can be found in Annex V
- Defined timelines for submission and publication of lay summaries (also known as plain language summaries) for adult and pediatric clinical trials are outlined in the regulation (12 months or 6 months after completion of clinical trial)
- The clinical trial lay-summary
  - Summary is short
  - Language is non-technical and understandable to a lay person
  - Graphs and tables are simplified
  - Will be made available by CTIS for public access
  - May already be made available by Sponsors on their corporate website(s)

Sponsor/CRO Readiness

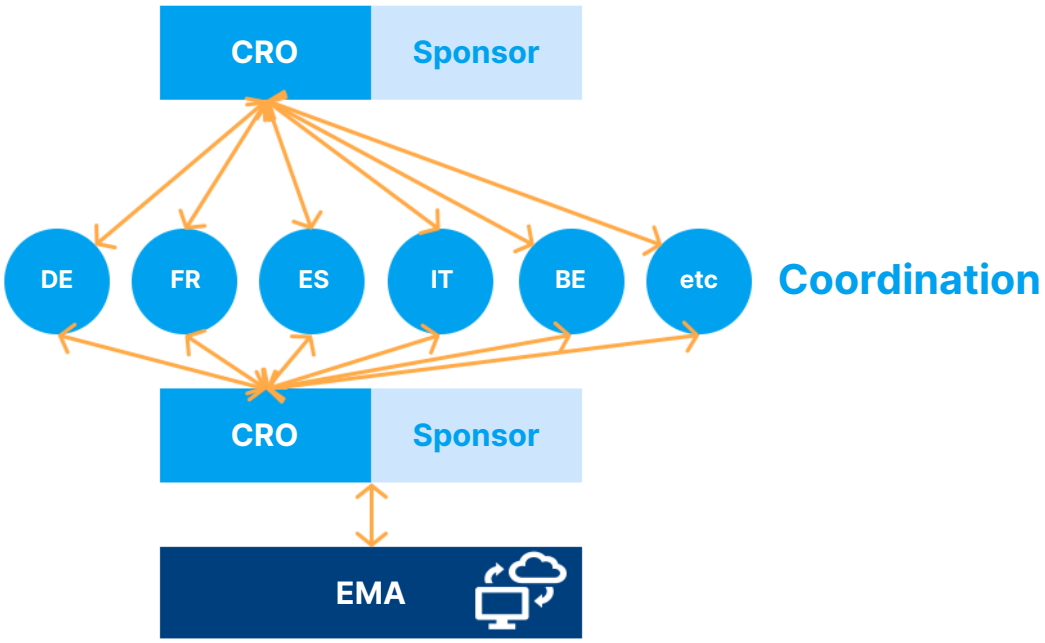
Challenges associated with operating clinical trials across two companies (Sponsor and CRO)

1 CRO works with many Sponsors and so must adapt ways of working to accommodate multiple Sponsor requirements	Only Sponsors have access rights to CTIS. For a CRO to interact with CTIS, user-rights must be administered and controlled by the Sponsor	Documentation associated with the single CTA submission (Part 1 and Part 2) reside in different IT systems within each company

CTD



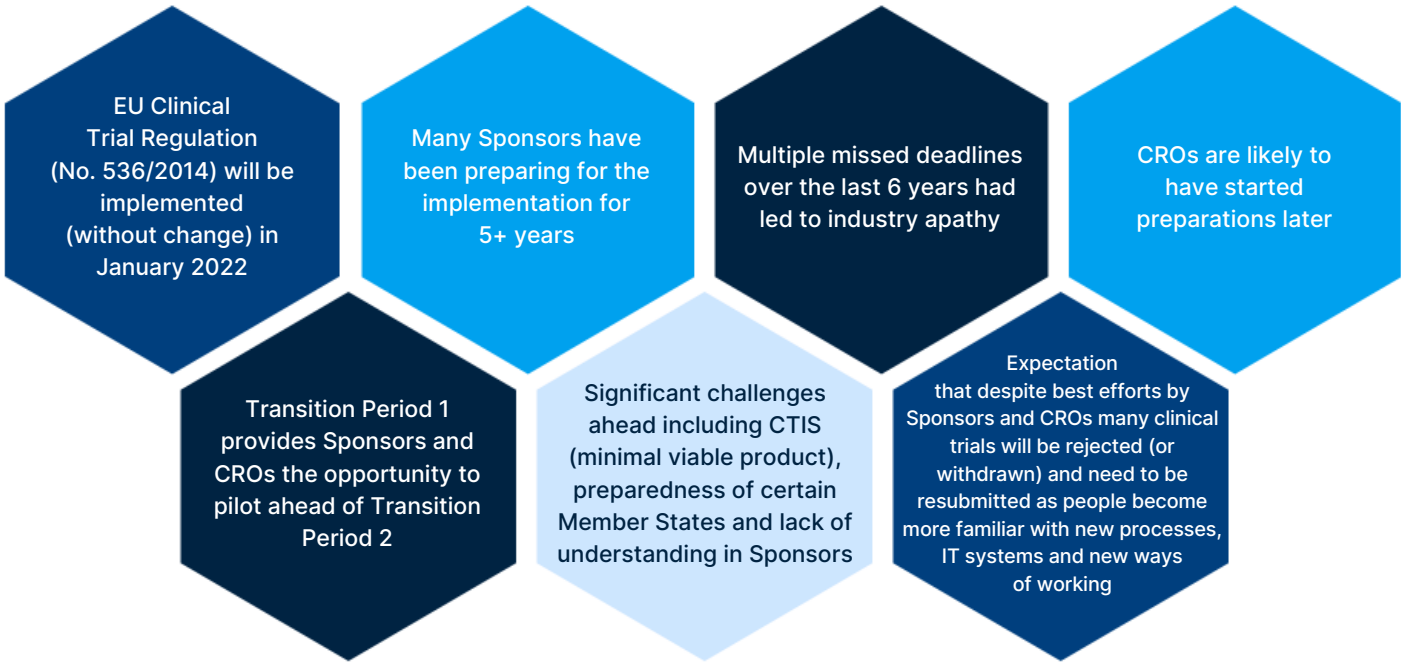
CTR



Readiness Assessment (Sponsor and CRO)

- Is the regulation understood?
- Are operational and logistical challenges understood
- Have process/structure/capability been prepared for the new ways of working and timelines?
- Have legal templates been updated?
- Have SOPs been updated?
- Do staff understand the change and have they been trained in preparation?
- Have staff undergone EMA-provided training on CTIS management?
- Has the portfolio been reviewed to determine the optimal regulatory framework for an individual trial (CTD of CTR)?
- Have trials that must transition been identified and preparations made for documentation?
- Have contracts, bid grids, MSAs and RFPs been updated to reflect the new regulatory framework?
- Have IT systems been adapted e.g. TMF folder structure to accommodate new ways of working?
- Has a first trial and study team been identified and mentored through the process?

Conclusion



2. INTRODUCTION TO LUCID CONSULTING

Lucid Consulting Value Proposition

"Lucid Consulting is a consulting firm focused on the life sciences industry. We bring a combination of deep health & life sciences expertise with the capabilities, discipline and resources of a top-tier management consulting firm."

- Focus on R&D and Medical Affairs with deep expertise and extensive experience drawn from both Consulting and from senior roles within Industry
- Ability to bring external perspectives, benchmarks and accelerators, from our experiences running complex transformational change programs in numerous companies and settings
- Recent experience working on implementation of cutting edge innovation into organisations including scientific communication platforms, RWE methodologies, scientific share of voice analysis, and other digital and sourcing solutions
- A team that seamlessly blends Consulting, Industry and Program Management capabilities with deep subject matter expertise
- A track record and a deep understanding of the importance of more patient centric approaches to the development and commercialisation of solutions and medicines that deliver value as defined by the patient

Lucid Consulting has extensive experience in addressing the critical issues that Biopharmaceutical teams are experiencing today

Transformational or incremental change program design & implementation...

... acknowledging the rapidly changing digital landscape

Lucid Consulting – about the author

Steve is Vice President of Consulting at Lucid Consulting. He has 20+ years of management and business consulting experience, working with top/mid-tier pharmaceuticals and CROs.

He specialises in enhancing cross-functional ways of working, process optimization, managing performance and delivering organizational change. His experience of consulting within Research & Development includes Clinical Development and Operations, Medical Affairs, Regulatory, Pharmacovigilance and Quality Assurance.

Steve previously led a group of internal consultants and project managers within Bayer Pharma R&D. Selected projects: co-leadership of R&D Culture Change, design and implementation of the Phase 1–4 clinical outsourcing strategy and leadership of preparations for the implementation of the EU Clinical Trial Regulation.

Previously, Steve was been Head of Development Consulting within the Syneos Strategy Advisory business, a Vice-President of Consulting at Kinapse and a Senior Manager at Deloitte. Prior to his consulting career he worked for a number of pharmaceutical companies including Johnson & Johnson in the US and UK.

He holds a Ph.D. from the Research School of Medicine at Leeds University and an MBA from Leeds University Business School. He is ProSci (change management) certified.

Contact:

Stephen Gunnigle PhD MBA Vice President, Lucid Consulting

About Lucid Consulting

Lucid Consulting is the consulting division in Lucid Group focused solely on the life sciences industry. We bring a combination of deep health & life sciences expertise with the capabilities, discipline and resources of a leading management consulting firm. Our consulting teams have worked extensively in R&D and Medical Affairs. We continue to focus on emerging trends, needs and best practices across the industry.