Il Project Management nel Drug Development
come meccanismo organizzativo
tra Casa Farmaceutica, Clinical Research Organization e Strutture Sanitarie

COMEDATA

sigma-tau

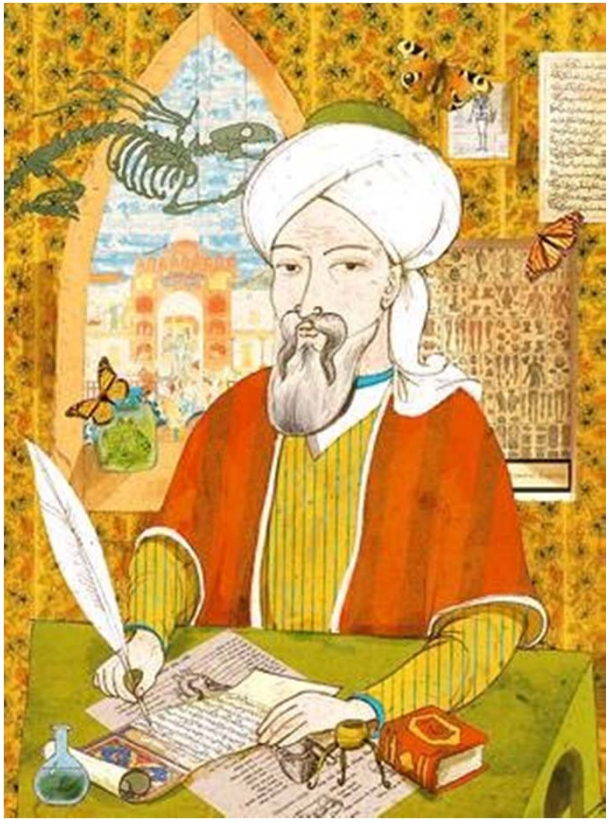
"GESTIRE, INNOVARE, CURARE.
Esperienze di Project Management in Sanità"

Emerenziana Iannoni (sigma-tau Industrie Farmaceutiche Riunite SpA)
Luca Angerame (Comedata)

Roma, 19 giugno 2012

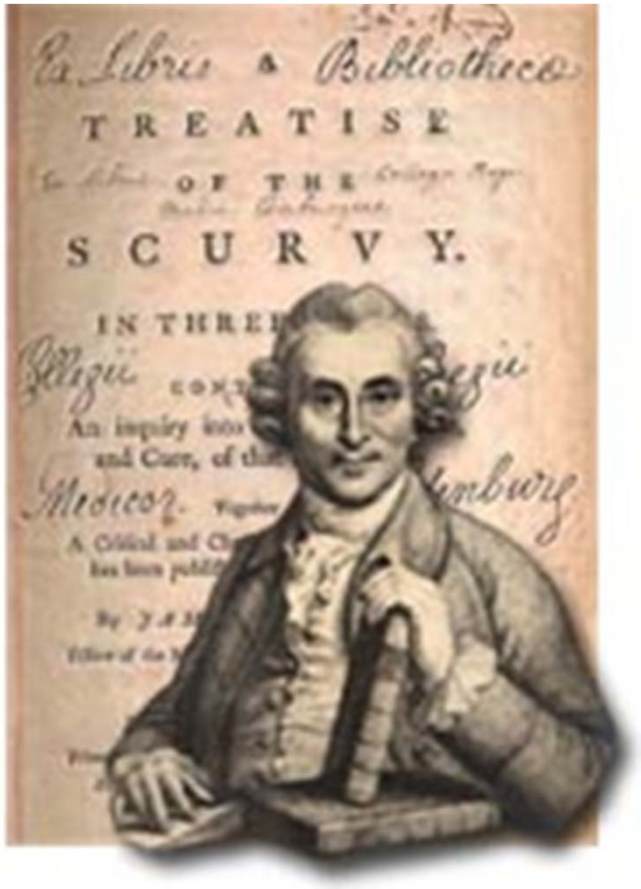
Introdusse per primo i trial clinici nel «Canone della Medicina», nel 1025.

Espose le regole per l'uso sperimentale e per i test con farmaci, scrivendo una guida precisa per la sperimentazione.



Avicenna (Balkh, 980 –Hamadan, 1037)

Uno dei più famosi trial clinici fu quello condotto da James Lind nel 1747 che portò a individuare l'acido ascorbico come cura dello scorbuto.



James Lind (Edimburgo 1716 -1794)

Il trial clinico

Final Study Report

Produzione farmaco sperimentale GMP

Analisi statistica

Table 8. Study Flow Chart

Day	0	1	2	3	7	14	21	28	35	42	Day of any Recurrent Parasitaemia
Informed Consent Signed	x										
Inclusion/Exclusion Criteria	x										
Demographic Data & Medical History	x										
Patient Symptoms	x	x	x	x	x	x	x	x	x	x	x
Physical Examination	x	x	x	x	x	x	x	x	x	x	x
Vital Signs (BP, HR & temp.)	x	x	x	x	x	x	x	x	x	x	x
Body Weight	x										
Blood Smear - thick and thin	x	x	x	x	x	x	x	x	x	x	x
PCR Sampling	x					x	x	x	x	x	x
Electrocardiogram	x		x		x			x[b]		x[b]	x
Haematology/Biochemistry	x			x	x[c]	x[d]		x		x	x
Adverse Event Recording	x	x	x	x	x	x	x	x	x	x	x
Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x
Study Medication	x	x	x								

If abnormal on a = Day 7, b = Day 28, c = Day 3, d = Day 7.

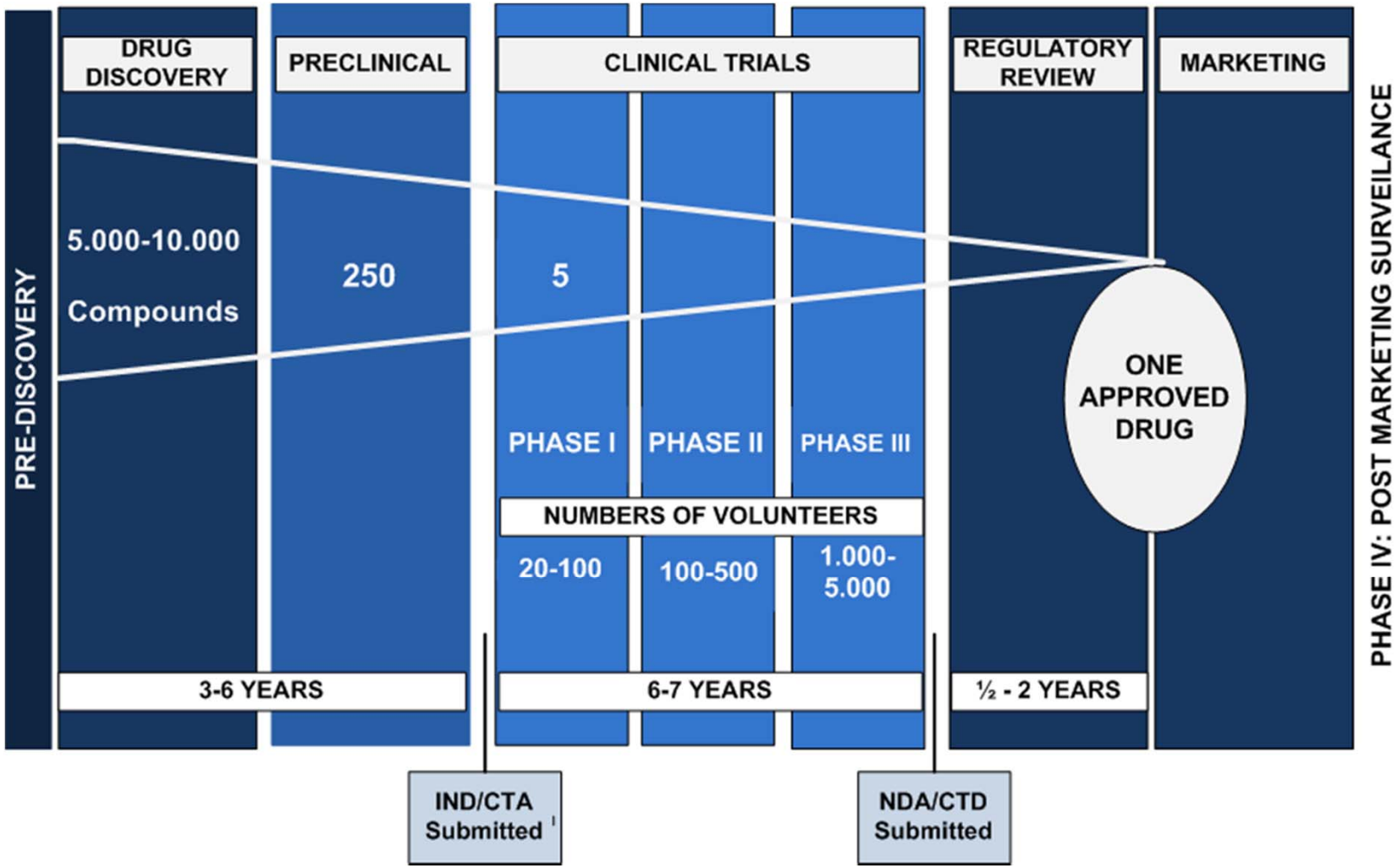
Protocollo di studio

Logistica e Farmacia

Consenso informato

Case Report Form

Processo di Sviluppo del Farmaco



The drug discovery and development process (adapted from Pharmaceutical Industry Profile 2009)

Le sfide per l'innovazione

- Aumento di costi e rischi nel processo di sviluppo del farmaco
- Aumento esponenziale di requisiti regolatori
- Maggiore competitività nel mercato
- Scadenza di molti brevetti per farmaci ad alta prescrittibilità

- Crollo del numero di farmaci in sviluppo
- Calo della produttività di R&D
- **Minori margini economici per fare ricerca**

La sfida del tempo

- Lo sviluppo di un nuovo farmaco dalla sintesi di un composto all'approvazione può richiedere dai 10 a 20 anni, con una media stimata di 10-12 anni

- La durata di questo processo è aumentata negli ultimi 20 anni a causa della maggiore complessità e durata dei trials clinici

- Le attività cliniche prendono il 60-70% del tempo di sviluppo totale

La sfida di costi e rischi

- I costi clinici sono il 63 % dei costi di sviluppo totale
- p(TS) totale: da 6% a 50% se si eliminano i rischi delle fasi cliniche

Lead Optimization	85%	85%
Pre-Clinical	69%	69%
Phase 1	54%	100%
Phase 2	34%	100%
Phase 3	70%	100%
Dossier Review	85%	85%
Overall Probability	**6%**	**50%**

Rielaborato da Nature Reviews Drug Discovery, Vol. 9, March 2010

Governare il processo di sviluppo del farmaco

per ridurre i rischi di insuccesso

è **conditio sine qua non**

come?

Il player

- Sigma Tau Industrie Farmaceutiche Riunite
- Primaria realtà farmaceutica in Italia
- Multinazionale di origine e proprietà italiana, sedi in 10+ paesi
- 1400 + dipendenti per 600+ mln € di fatturato
- **R&D full cycle: dalla Ricerca al Mercato**
  - **Questo ne fa una delle pochissime Integrated Pharmaceutical Company italiane**

Lo scenario di R&D

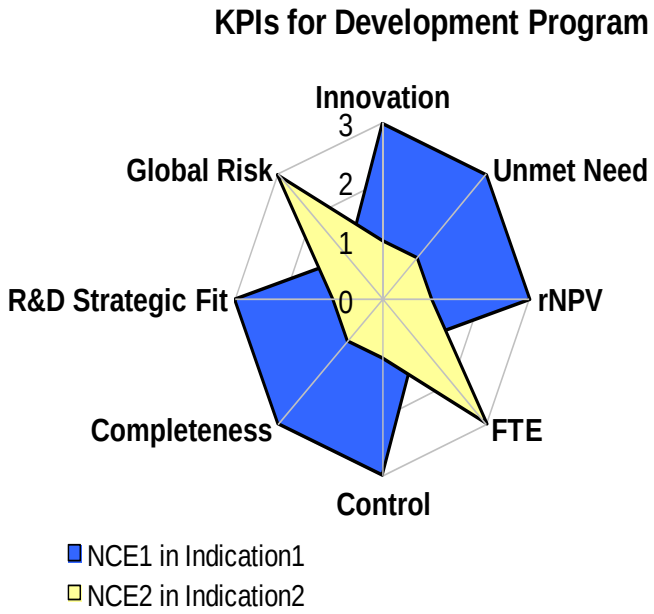
Strengths	Weaknesses
Dipartimento R&D full-cycle Forti competenze interne	Difficoltà nel rispetto delle finestre di opportunità Difficoltà di approccio dei team interfunzionali

Opportunities	Threats
Nicchie di medical needs affrontabili con innovazioni di processo Time frame adeguato	Margini di mercato in diminuzione Declassificazione della rimborsabilità di alcuni prodotti Genericazione di molecole importanti

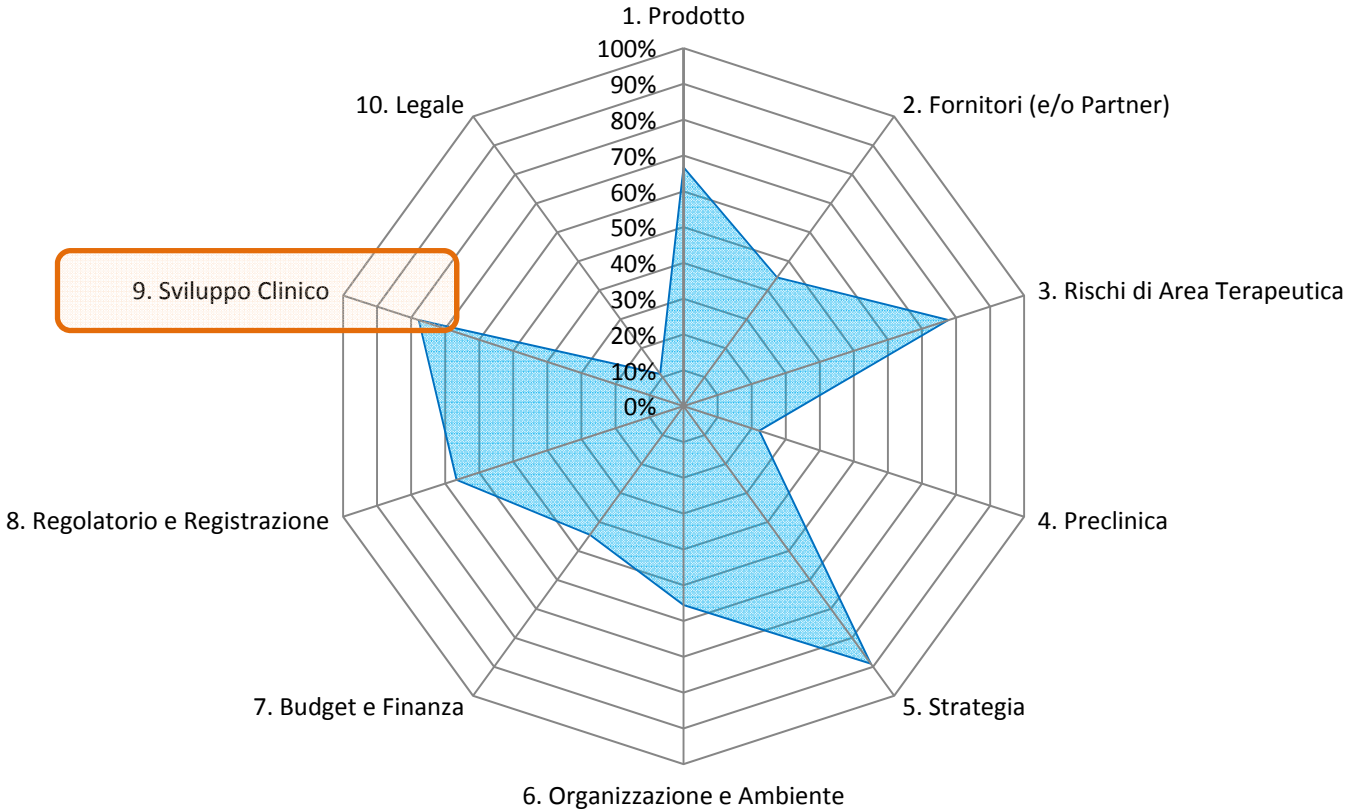
Key Performance Indicators

- Qualitative
  - Innovation
  - Medical Need

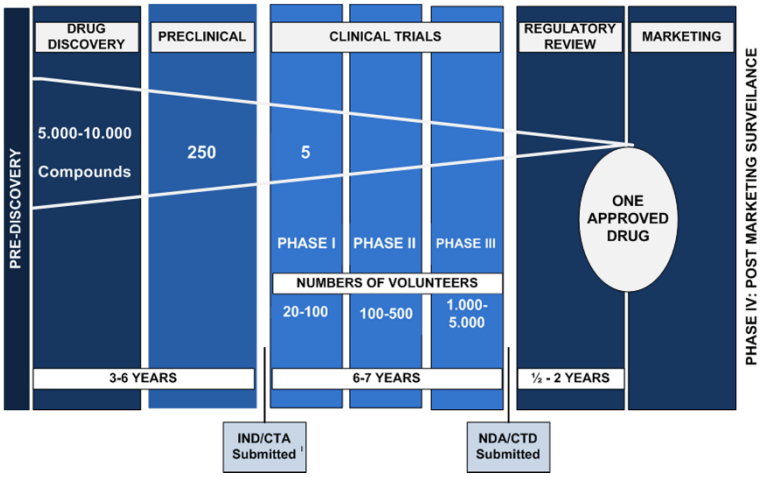
- Quantitative
  - rNPV
  - Control
  - FTEs
  - Completeness
  - Strategic Fit
  - Risk

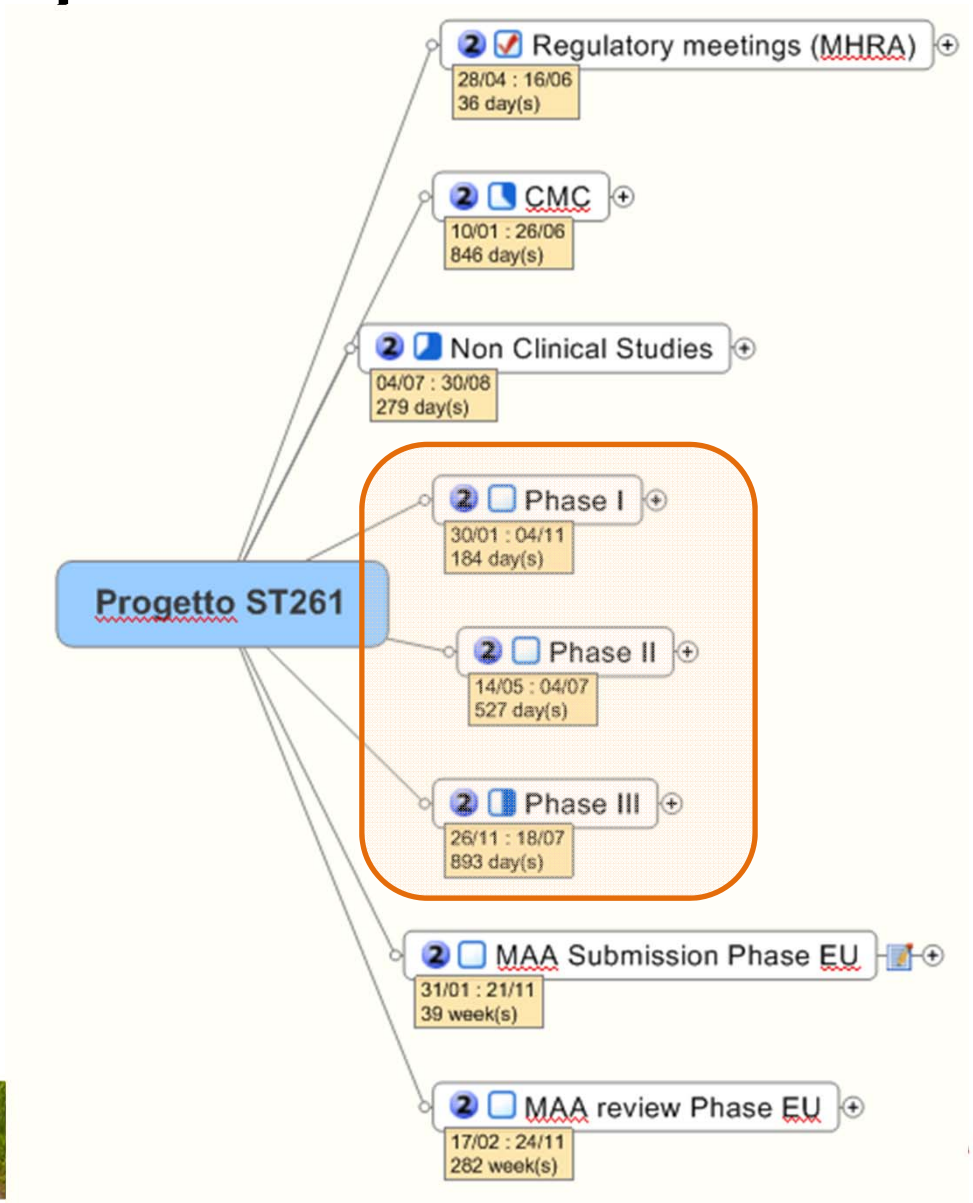


Indicatore di Rischio



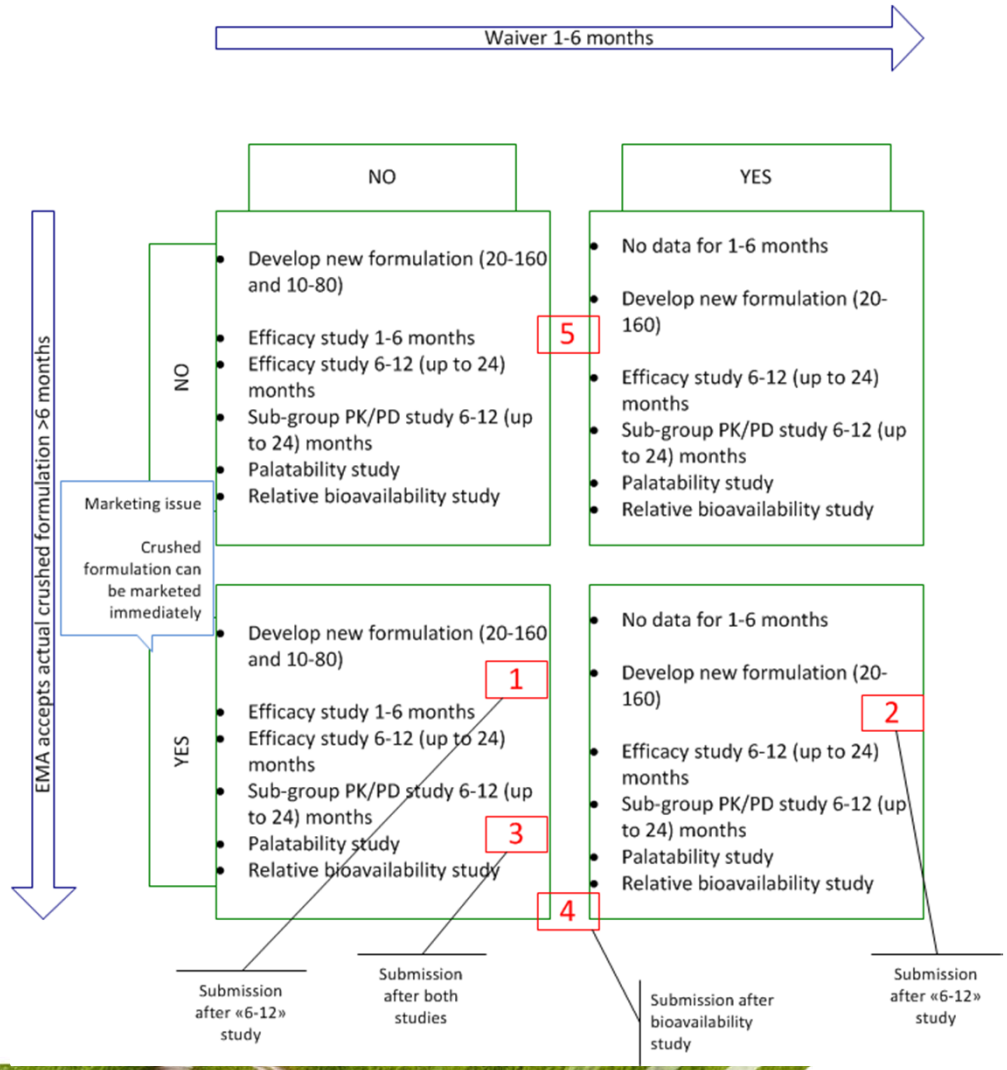
Drug Development: WBS



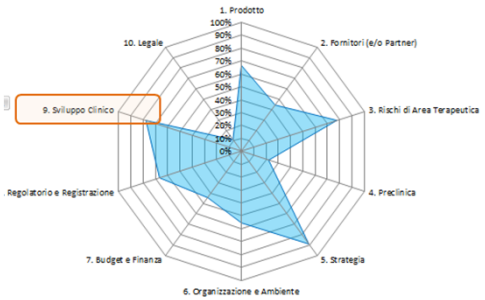


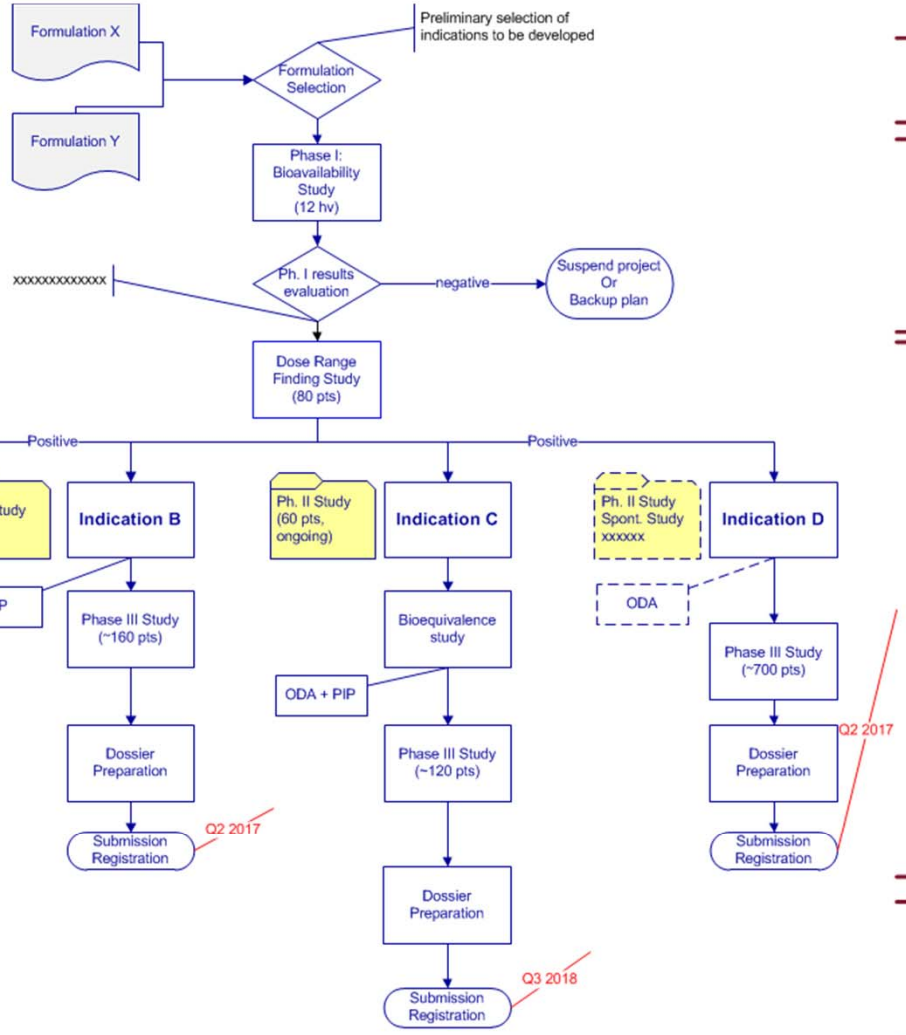
From Strategy to Deploy + Services

Roadmap to Clinical Development Plan



Roadmap to Orphans

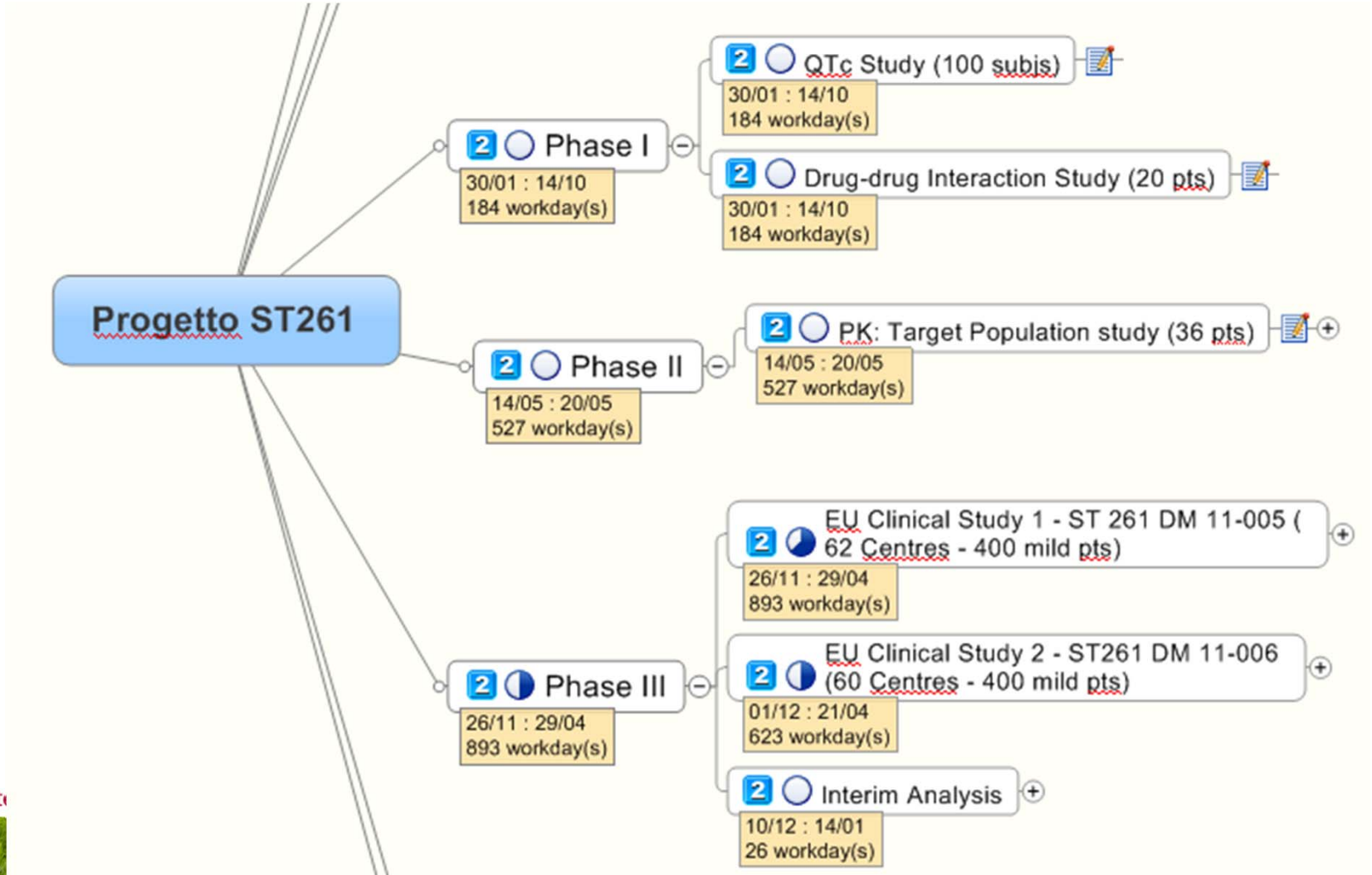




From Strategy to De

COMEDATA

Piano di Sviluppo Clinico

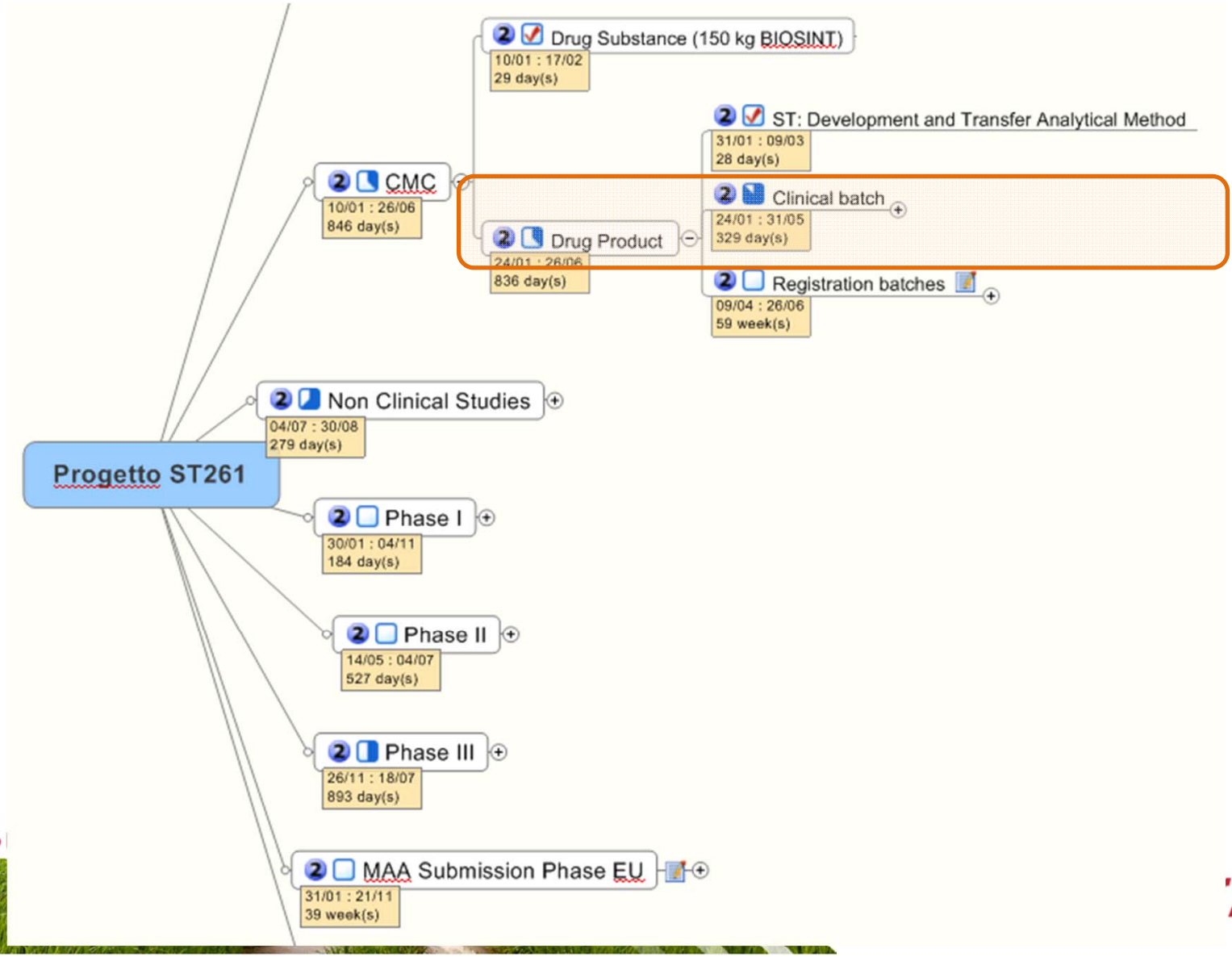


From Strat

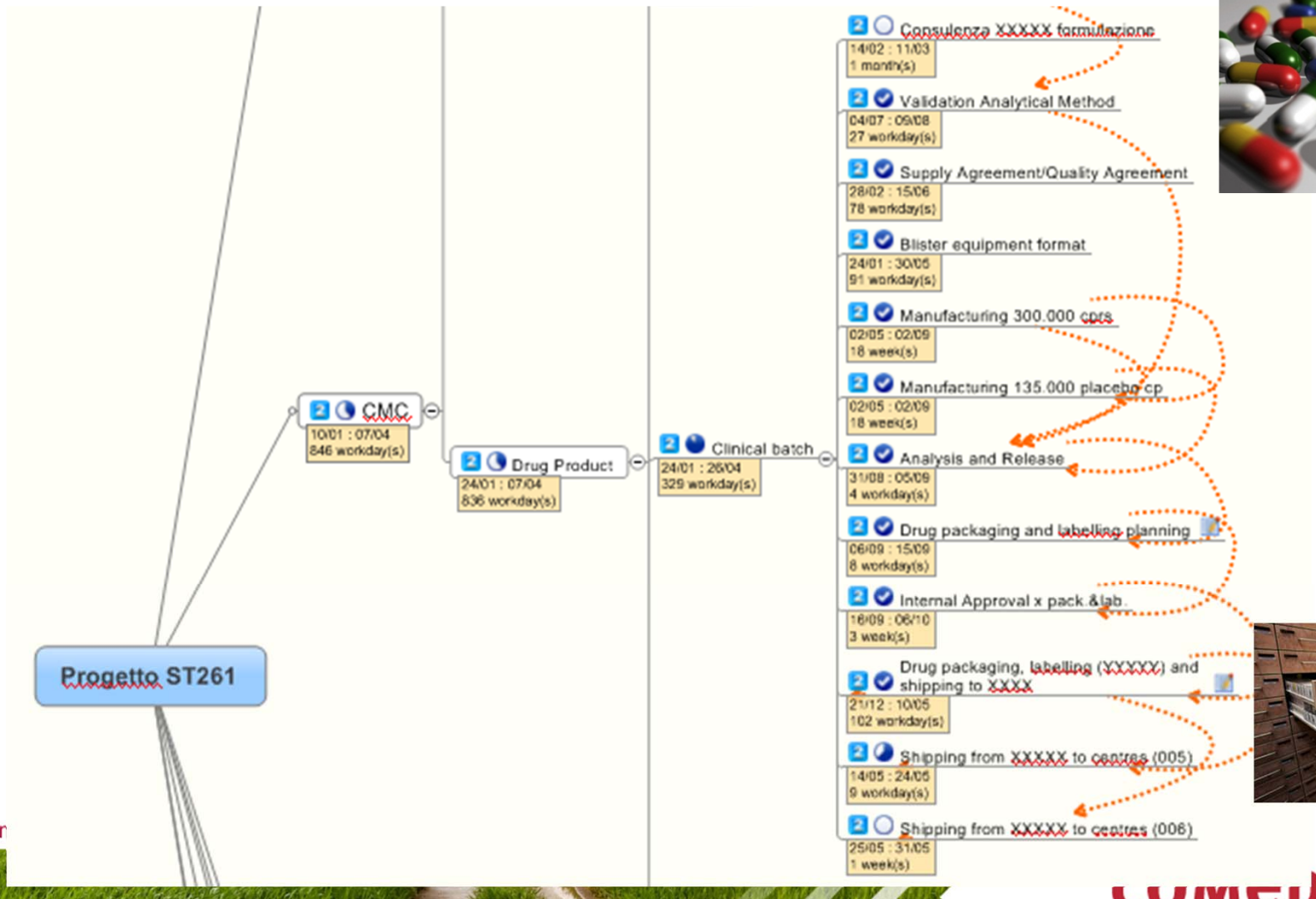
Attori coinvolti

- Sponsor
- Autorità Regolatorie Nazionali
- Direzioni Sanitarie locali
  - Farmacia
  - Centri Sperimentali
    - Sperimentatori
    - Pazienti
- Comitati Etici locali
- CRO
- Eventuali cosponsor

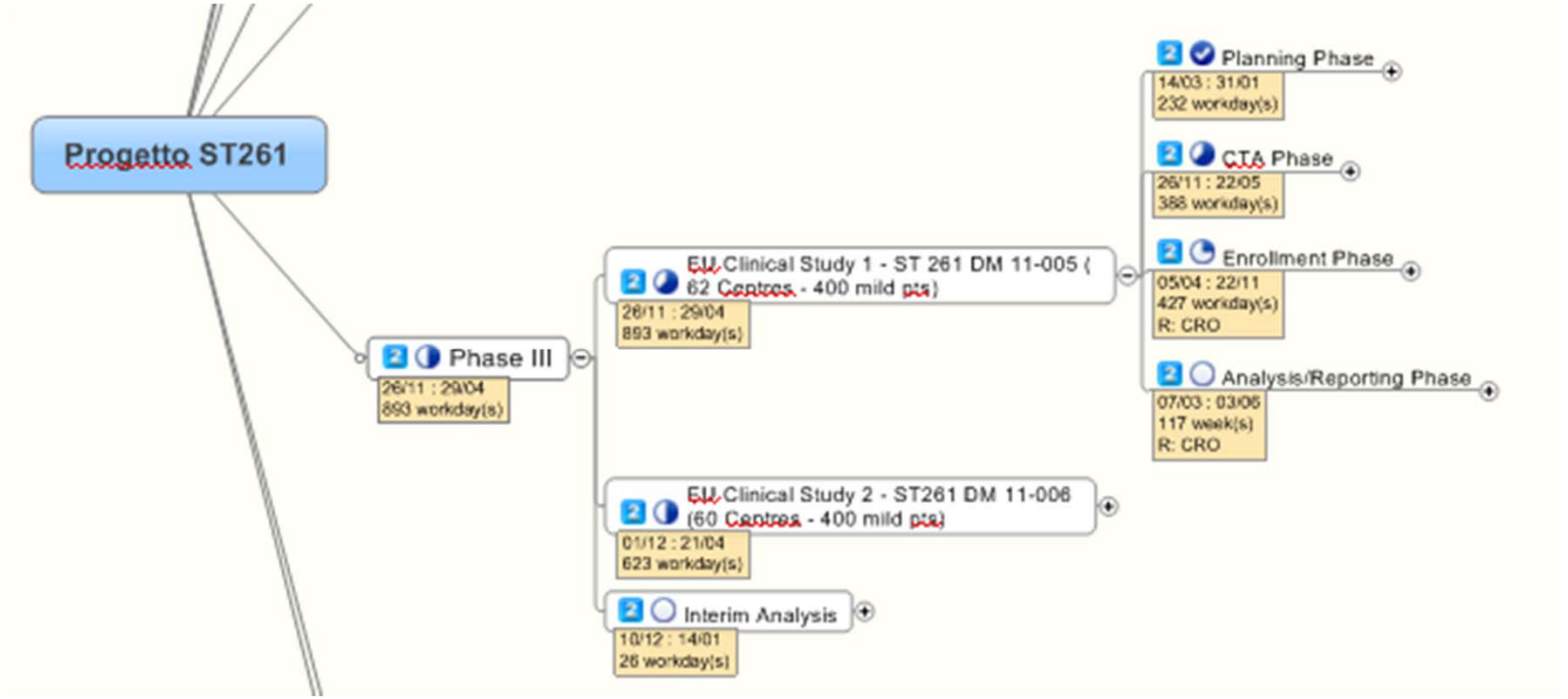
WBS: elementi clinici



Clinical Batch



Studio Clinico



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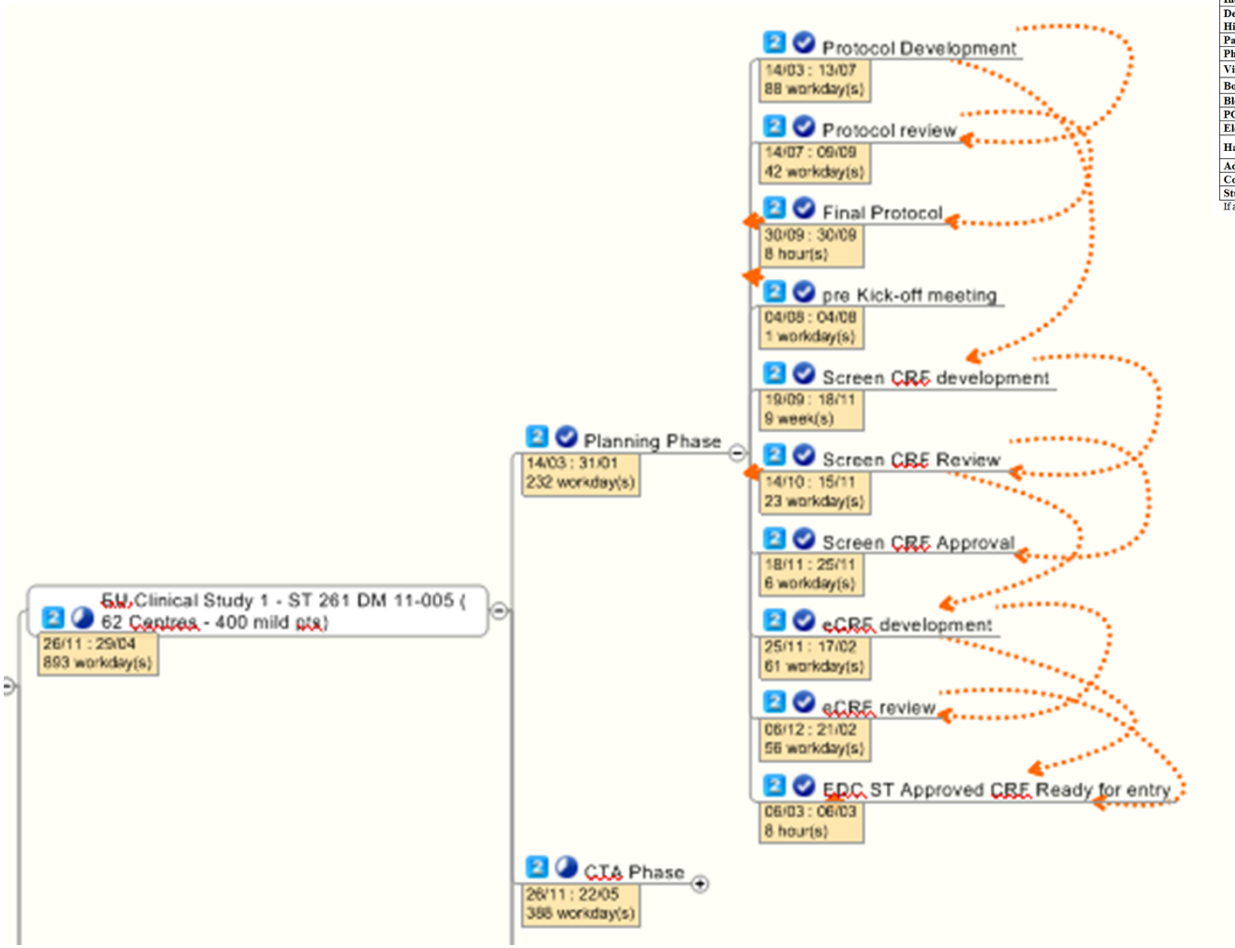

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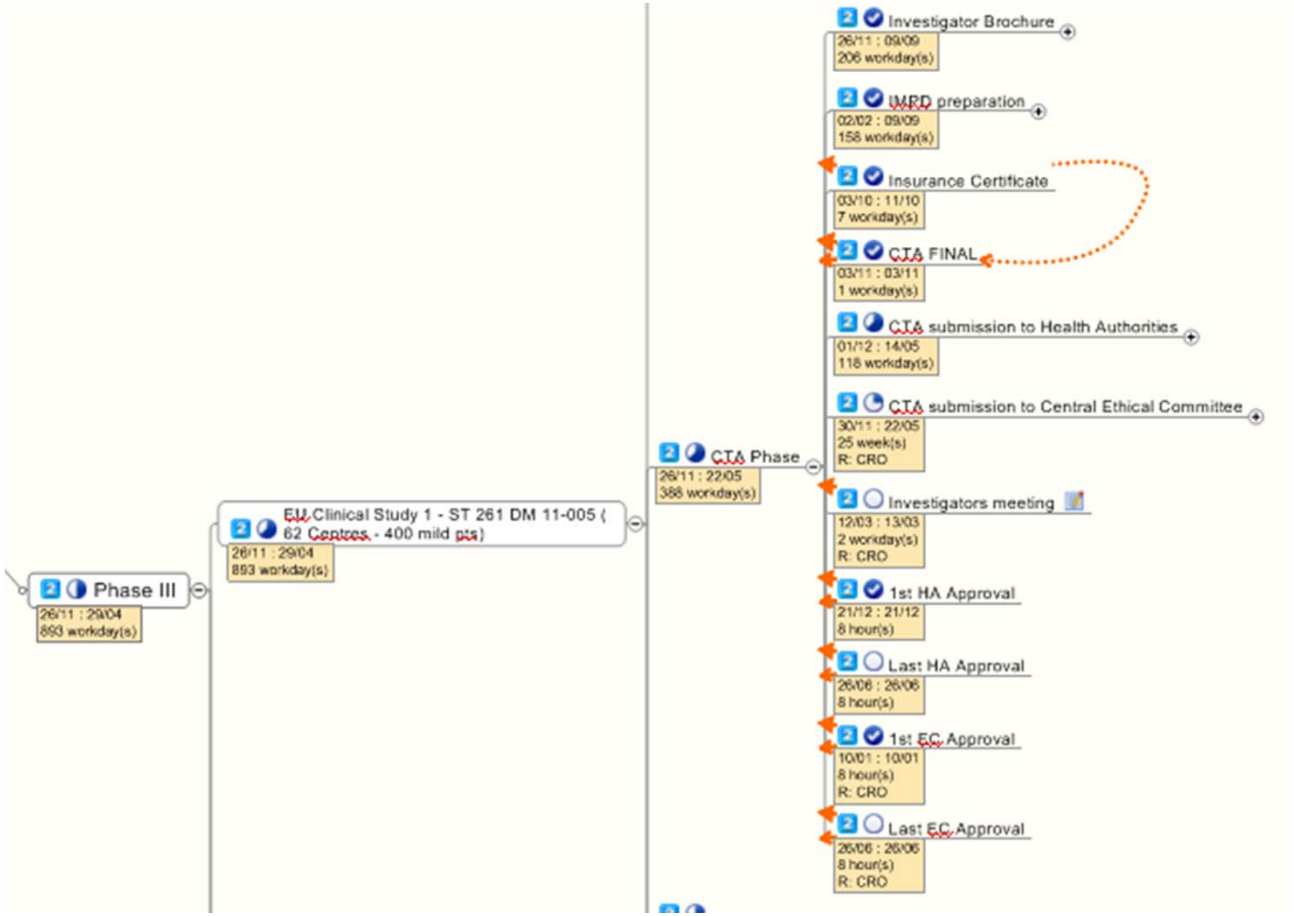
Demographic Data & Medical History	x										
Patient Symptoms	x	x	x	x	x	x	x	x	x	x	x
Physical Examination	x	x	x	x	x	x	x	x	x	x	x
Vital Signs (BP, HR & temp.)	x	x	x	x	x	x	x	x	x	x	x
Body Weight	x										
Blood Smear - thick and thin	x	x	x	x	x	x	x	x	x	x	x
PCR Sampling	x					x	x	x	x	x	x
Electrocardiogram	x		x		x			x[a]		x[b]	x
Haematology/Biochemistry	x			x	x[c]	x[d]		x		x	x
Adverse Event Recording	x	x	x	x	x	x	x	x	x	x	x
Concomitant Treatments	x	x	x	x	x	x	x	x	x	x	x
Study Medication	x	x	x								

If abnormal on a = Day 7, b = Day 28, c = Day 3, d = Day 7.

From Strategy to Deploy + Services

COMEDATA

Studio Clinico



Studio Clinico

Phase III
26/11 : 18/07
893 day(s)

EU Clinical Study 1 - ST 261 DM 11-005 (62 Centres - 400 mild pts)
26/11 : 18/07
893 day(s)

Enrollment Phase
05/04 : 08/01
427 day(s)
R: CRO

- First initiation visit — 05/04 : 05/04, 1 day(s), R: CRO
- IP release — 25/05 : 07/06, 2 week(s)
- First Site Activated — 25/05 : 25/05, 1 day(s)
- 1st patient IN — 13/06 : 13/06, R: CRO
- Last Site Activated — 24/07 : 24/07, R: CRO
- Last patient IN — 10/09 : 10/09, R: CRO
- Last patient OUT — 09/11 : 09/11, R: CRO
- Last Site Closed — 08/01 : 08/01, R: CRO

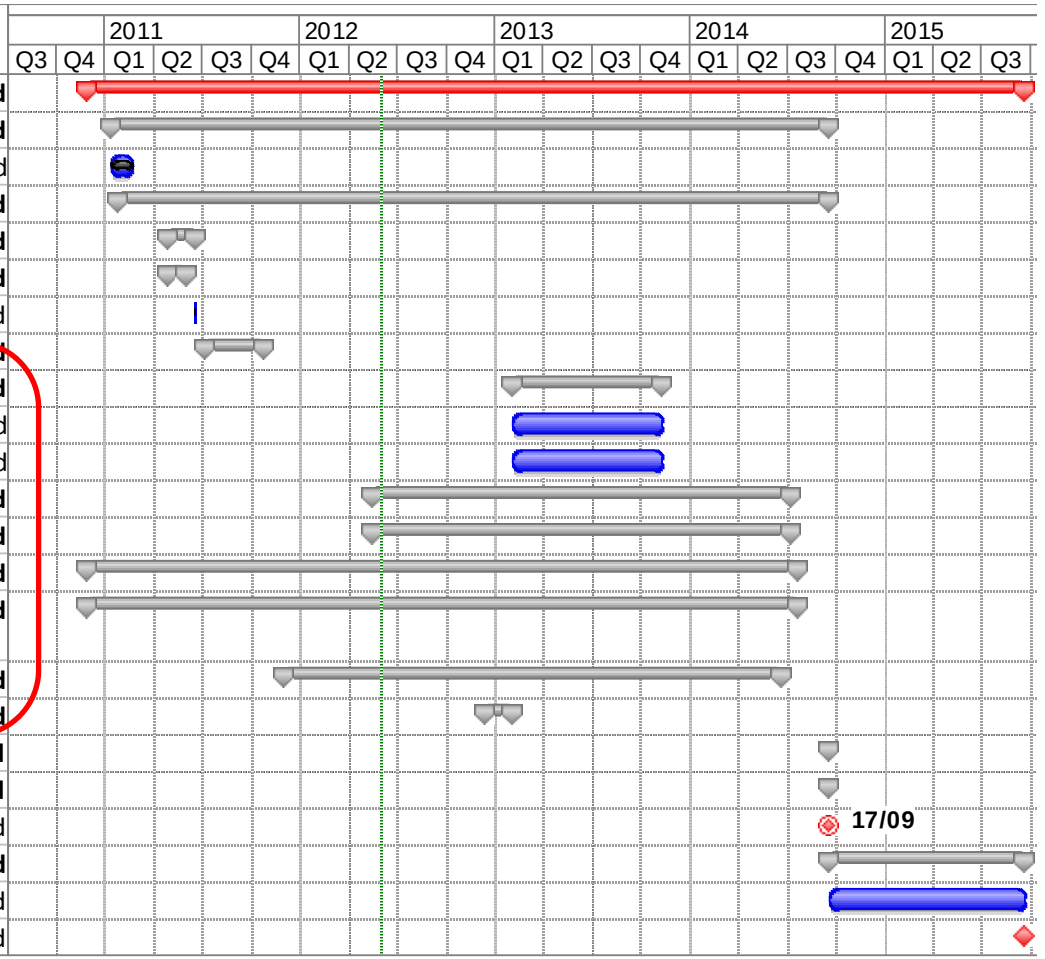
Analysis/Reporting Phase
07/03 : 18/07
117 week(s)
R: CRO

- Database planning & validation — 07/03 : 27/04, 38 day(s), R: CRO
- Database freezing — 29/11 : 29/11, R: CRO
- Statistical analysis — 02/12 : 10/04, 86 day(s), R: CRO
- Draft Report — 11/04 : 20/06, 51 day(s)
- Draft Report review — 23/06 : 18/07, 1 month(s)
- ST Approved Clinical Study Report — 18/07 : 18/07

COMEDATA

Master Plan

WBS	Task Name	Duration
0	**ID23 - ST261**	**1160 d**
1	**CMC**	**889 d**
1.1	Drug Substance	29 d
1.2	**Drug Product**	**879 d**
2	**Regulatory meetings (MHRA)**	**36 d**
2.1	**Briefing Package (BP)**	**24 d**
2.2	MHRA Scientific Advice Meeting	2 d
3	**Non Clinical Studies**	**65 d**
4	**Phase I**	**184 d**
4.1	**QTc Study (100 subjs)**	184 d
4.2	**Drug-drug Interaction Study (20 pts)**	184 d
5	**Phase II**	**527 d**
5.1	**PK: Target Population study (36 pts)**	**527 d**
6	**Phase III**	**893 d**
6.1	**EU Clinical Study 1 - ST 261 005 (62 Centres - 400 mild pts)**	**893 d**
6.2	**EU Clinical Study 2 - ST261 006 (60 Centres - 400**	**623 d**
6.3	**Interim Analysis**	**26 d**
7	**MAA Submission Phase EU**	**1 d**
7.1	**CTD Preparation**	**1 d**
7.2	CTD Submission	0 d
8	**MAA review Phase EU**	**239 d**
8.1	CTD Review	365 ed
8.2	**Approval**	0 d

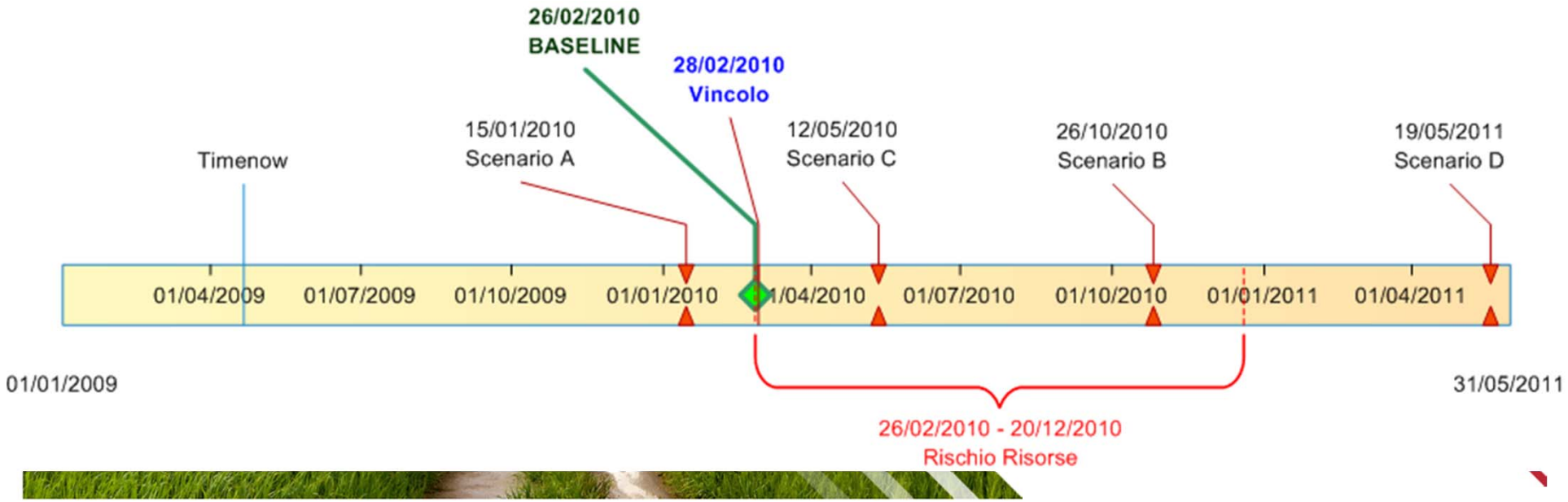


From Strategy to Deploy + Services

COMEDATA

Master Plan
scenari risk adjusted

	Ottimistico	Pessimistico
Risorse entro free float	**A** **15 gennaio 2010**	**B** **26 ottobre 2010**
Risorse oltre free float	**C** **12 maggio 2010**	**D** **19 maggio 2011**



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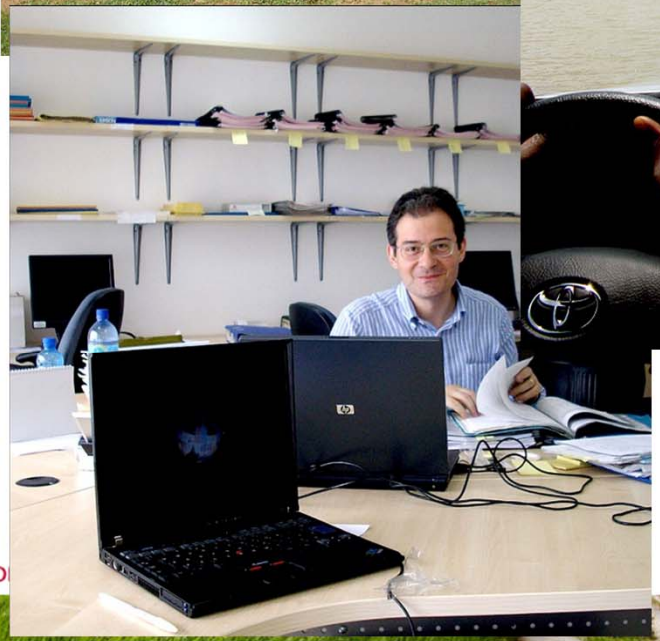
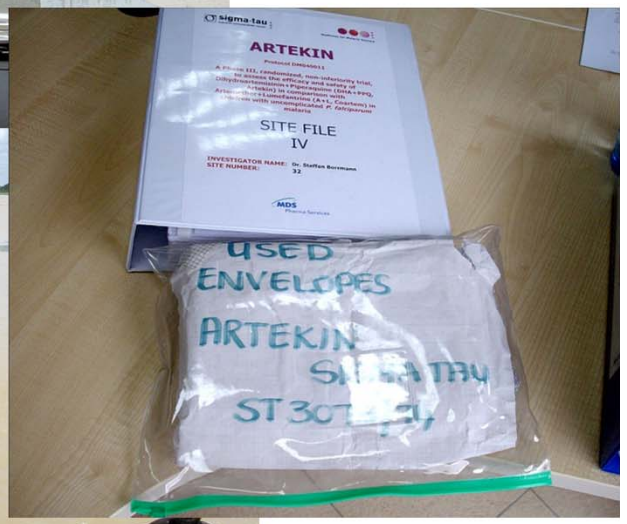
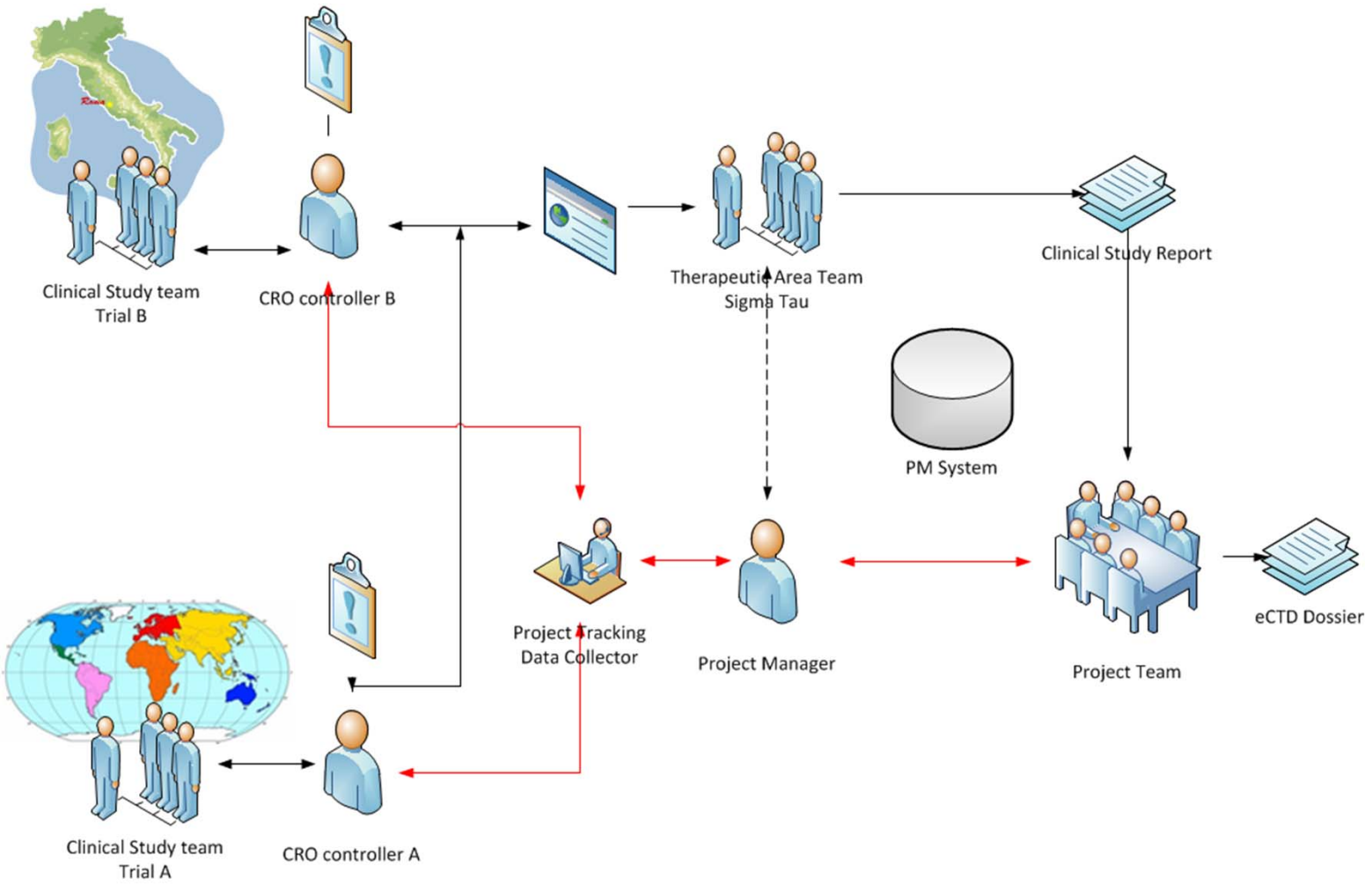
Trial Africa Ph.III (Kenya)





Processo di Controllo



Eurartesim

Piano di Controllo Avanzamento

Rif. Baseline 1 r4

Keasys

N°	Rilevazione	Timenow	Piani	Note
Av. 25	20-Apr-09	17-Apr-09	Regolatorio PreClinica CMC	Monitoraggio Contingency Monitoraggio 3.2.S - CMC
Av. 26	27-Apr-09	24-Apr-09	~~Product~~ PreClinica CMC	Monitoraggio Contingency Monitoraggio 3.2.S - CMC
Av. 27	4-May-09	1-May-09	Regolatorio	Interviste
Av. 28	11-May-09	8-May-09	~~Product~~ Regolatorio CMC	Monitoraggio 3.2.S - CMC
Av. 29	18-May-09	15-May-09	Product Regolatorio CMC	Monitoraggio 3.2.S - CMC
Av. 30	25-May-09	22-May-09	Product Regolatorio CMC	Monitoraggio 3.2.S - CMC
Av. 31	1-Jun-09	29-May-09	Product Regolatorio CMC	Monitoraggio 3.2.S - CMC
Av. 32	8-Jun-09	5-Jun-09	Product Regolatorio Filing	Interviste Monitoraggio 3.2.S - CMC

Criterio
Eventi pond
Proporziona
Proporziona
Unità finite

2.4 *Indi*

2.4.1 Pre

Le attività s

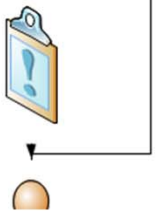
Filtro per at

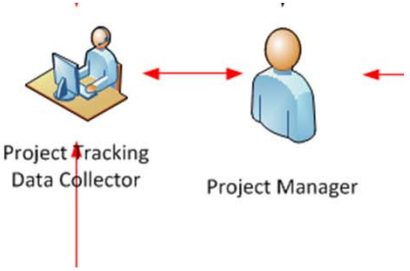
2.4.2 Cli

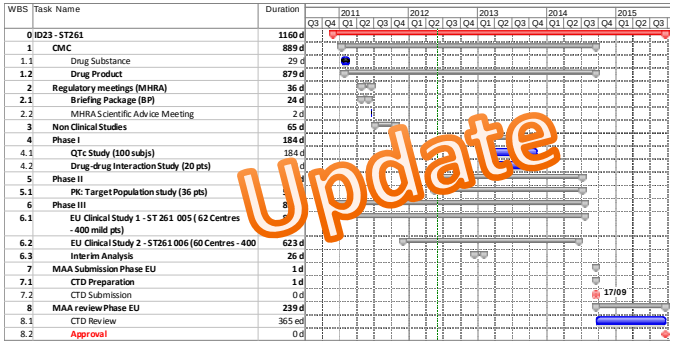
Intervallo d
salvo period

COMEDATA

Processo di Controllo







Update

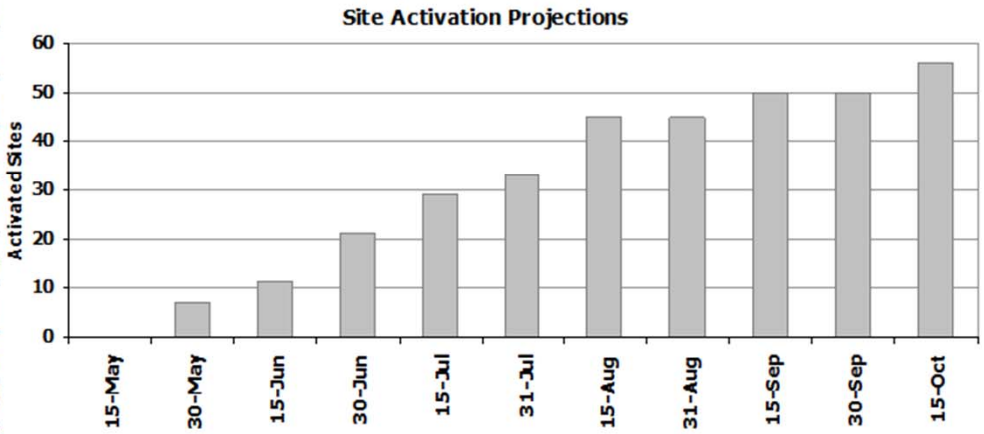
2.0 Metrics

2.1 Subject Recruitment Months

Country	Target Sites	Approved Sites	Activated Sites	Target[1]	Current[2]	Variance[3]
Belgium	5	3	2	60		
Czech Rep.	9	9	2	96		
Israel	8	8	0	96		
Italy	7	6	0	72		
Netherlands	4	3	0	60		
Romania	7	7	0	72		
Russia	12	12	0	14		
Slovakia	8	8	4	60		
Totals:	**60**	**56**	**8**	**66**		

Baseline Subject Recruitment Months of 720 is based on original assumptions, p
1 Target SRM based on Project Start Up Plan, assuming all documents will be re
2 Current Subject Recruitment Months is based on data from 04MAY2012, assu
3 Variance = (Current – Target) / Target

2.3 Site Activations Projections, cumulative



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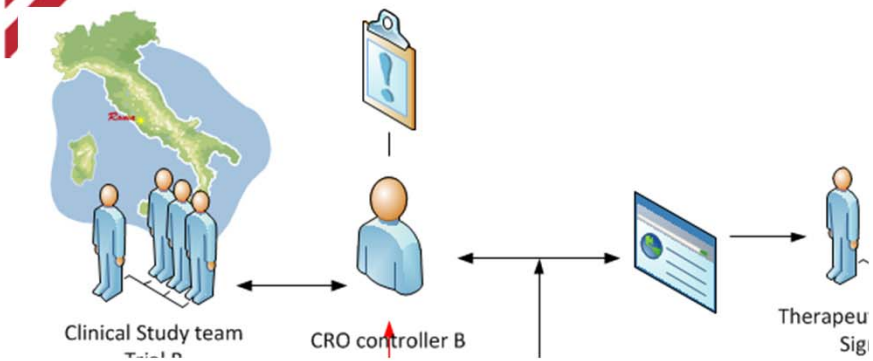

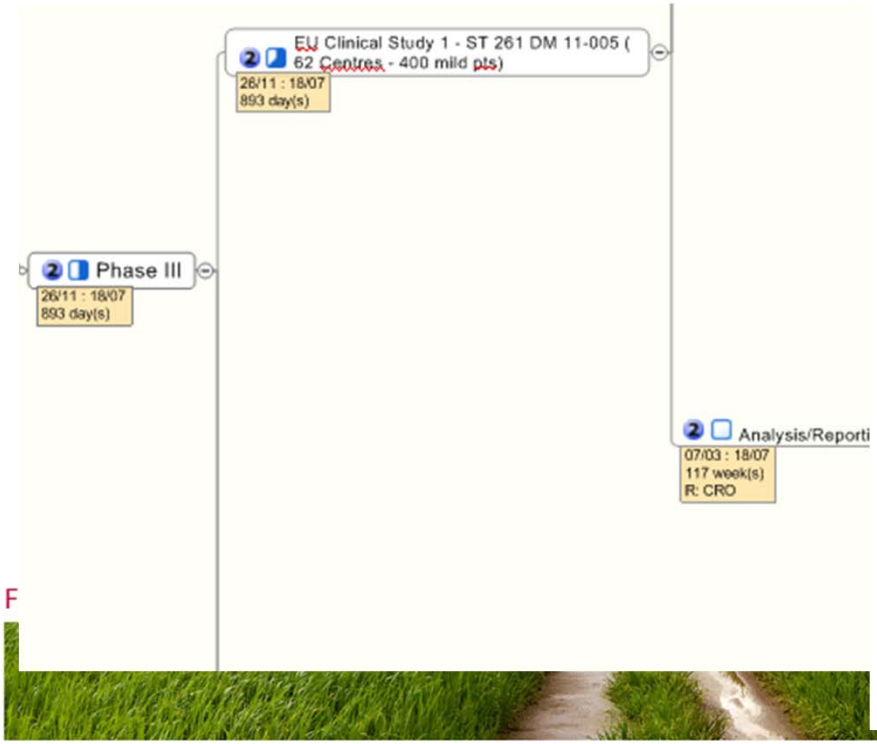

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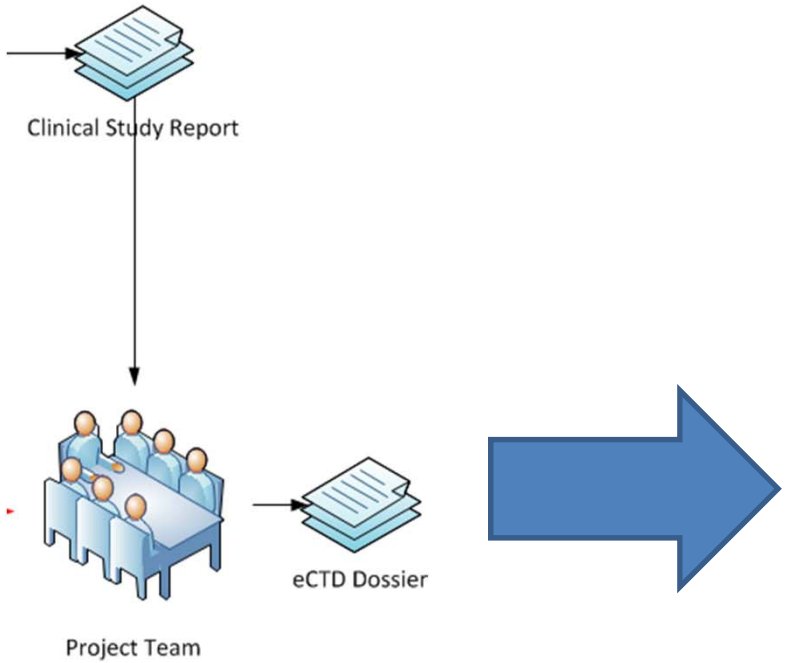
CLINICAL STUDY REPORT

A Phase I/II, Open-Label, Pharmacokinetic, Safety and Efficacy Study of (Artekin™), 40 mg Dihydroartemisinin/ 320 mg Piperaquine Phosphate Tablets in Adult Malaria Patients (*P. Falciparum*)

Product:	Artekin™ (Dihydroartemisinin/ Piperaquine)
Pharmaceutical form:	Tablets containing 40mg Dihydroartemisinin and 320mg Piperaquine
Indication:	Acute uncomplicated *P. falciparum* malaria
Phase of development:	I/II
Sponsor	Sigma-Tau Industrie Farmaceutiche Riunite S.p.A. Roma, V. le Shakespeare 47, Italia.
Protocol Number	ST3073-ST3074 DM04009
Study start date:	29 August 2005
Study completion date:	09 January 2006
Co-ordinating Investigator:	Professor Sornchai Looareesuwan
Sponsor Signatory	Dr Marco Corsi, Medical Director

"This study was conducted in accordance with the World Medical Association Declaration of Helsinki and ICH Topic E6, Guideline for Good Clinical Practice, including the archiving of essential documents".

Step Finale: Dossier



Task Name
Module 1 (Background)
1.0 Cover Letter
1.2 Application Form
1.3.1 PI (SPC, label, leaflet) (Adults/Children)
1.3.2 Mock-up
1.4 Info about Experts
1.6 Environmental Risk Assessment
1.8 Info relating to Pharmacovigilance
1.9 Info relating to Clinical Trials
Hyperlinking and Publishing (excluding final SPC)
Module 2 (Summaries)
2.2 Introduction
2.3 Quality Overall Summary
2.4 Non-Clinical Overview
2.5 Clinical Overview
2.6 Non-Clinical Summary
2.7 Clinical Summary
Hyperlinking and publishing
Module 3 (Quality)
3.2.S Drug Substance
3.2.P Drug Product
3.2.R Regional Information (EU/US)
Hyperlinking and publishing
Module 4 (Non clinical reports)
4.2.1 Pharmacology
4.2.2 Pharmacokinetics
4.2.3 Toxicology
Hyperlinking and publishing
Module 5 (Clinical reports)
5.2 Tabular listing of all clinical studies
5.3.1 Biopharmaceutic studies (BA/BE/Methods)
5.3.2 PK with human materials
5.3.3 Human PK
5.3.4 Human PD (Literature)
5.3.5 Efficacy/Safety
5.3.6 Post-marketing
5.3.7 CRFs/patient list.
5.4 Literature

From Strategy

Criticità di clinical Study vs Dir. Sanitaria

1. Problematiche legate sia ai contenuti e ai tempi di formalizzare del **contratto**

2. Coinvolgimento non standardizzato della **farmacia** nella gestione del farmaco sperimentale.

3. Non sufficiente coinvolgimento delle Direzioni Sanitarie nella valutazione del **personale** necessario per il corretto svolgimento delle sperimentazioni cliniche.

Considerazioni finali

- Il Project Management è imprescindibile per il governo di contesti complessi
- Sono efficaci anche metodi di base, applicati rigorosamente e sistematicamente
  - Diventa un meccanismo organizzativo fondamentale per tutto il progetto di sviluppo
- Si devono rispettare le condizioni di efficacia di base
  - Il Master Plan è l'unico scheduler per le risorse coinvolte, su base quotidiana
  - Il Master Plan va aggiornato regolarmente
  - Eseguire rigorosamente la fase di controllo del progetto
- Il project management non deve essere uno sforzo eroico, ma un metodo strutturale
- E' importante prima governare il processo, poi implementare i tool più adatti

Fine

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