



FICOG | Federation of Italian Cooperative
Oncology Groups

INTRODUZIONE ALLA RICERCA INDIPENDENTE
Focus sull'immuno-oncologia
23 e 30 giugno 2021

TEAM DI RICERCA: COME VALORIZZARE LA DIVERSITA'

Stefano Stabile - Ospedale Niguarda, Milano



Ospedale Niguarda
Cancer Center

Sistema Socio Sanitario



Regione
Lombardia



GIDM

Coordinatori di
Ricerca Clinica

Gruppo Italiano Data Manager

Sempre maggiore complessità negli studi clinici

BIOBUSINESS BRIEFS

 TRIAL WATCH

Trends in clinical trial design complexity

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NATURE REVIEWS | DRUG DISCOVERY

VOLUME 16 | MAY 2017 | 307

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The analysis is based on 9,737 clinical trial protocols that received ethics review board approval between 2001 and 2015, drawn from Medidata's PICAS database, which contains detailed protocol and investigative site contract data from more than 170 global pharmaceutical and biotechnology companies

Design elements associated with executional feasibility — including the number of procedures performed, the number of planned study volunteer visits, the work effort to administer procedures and the cost per study volunteer visit — were evaluated and compared across two time periods — 2001–2005 and 2011–2015 — separated by 10 years to characterize trends. This approach

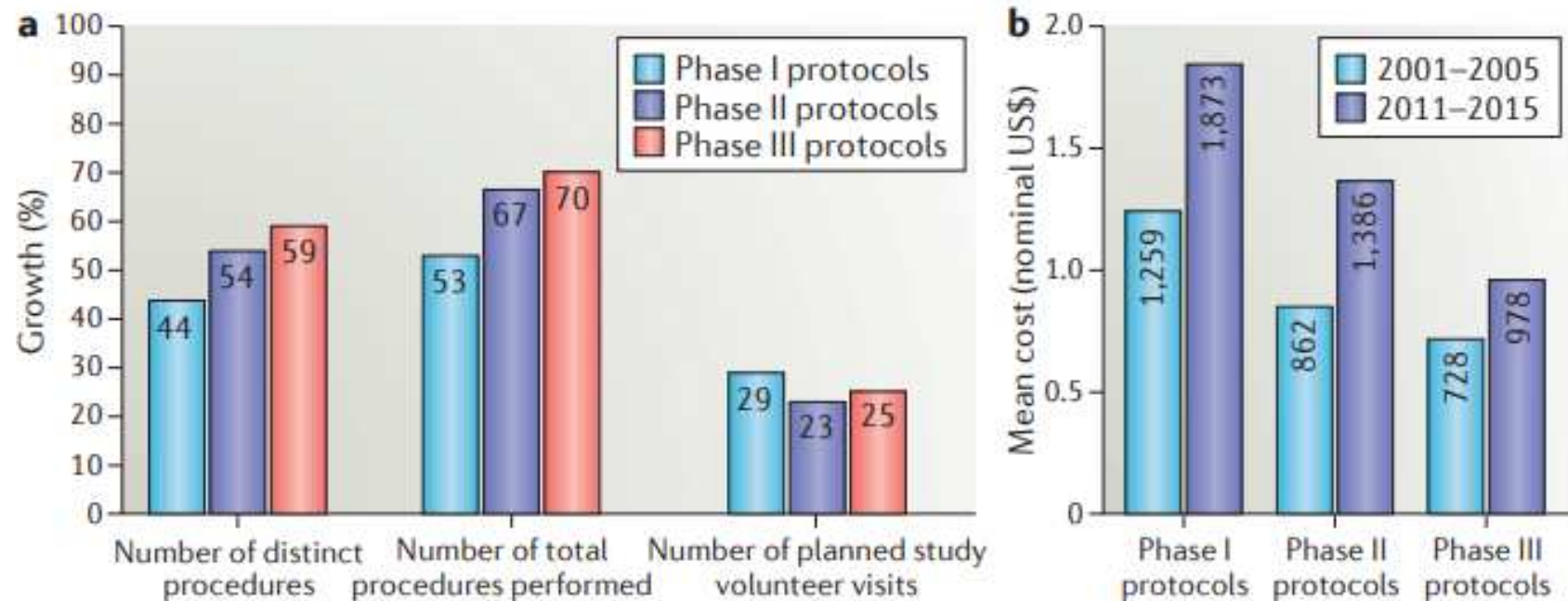


Figure 1 | Trends in the complexity and costs of clinical trials. a | Growth rates for protocol design metrics between 2001–2005 and 2011–2015. **b** | Cost per volunteer visit for the same two periods. Increases in protocol complexity have offset cost savings from procedural efficiencies and technology improvements. See [Supplementary information S1](#) (box) for details.

“ The work required to administer phase I, II and III protocols at investigative sites also increased substantially over the 10-year time period “



Procedure Centralizzate



Fase III, in aperto

- Visita 1 (Week 1D1): 4 KIT: 2 pre, 1 fine infusione, 1 post 2-8 ore
- Week 1D2: 1 kit pre
- Visita 2 (week 3): 1 KIT pre
- Visita 3 (week 5): 1 KIT pre
- Visita 4 (week 7 Day 43): 3 KIT: 1 pre, 1 fine infusione, 1 post 2-8 ore
- Visita 5 (week 9 Day 57): 1 KIT pre
- Visita 6 (week 11 Day 71): 1 KIT pre
- Visita 7 (week 13 Day 85): 3 KIT: 1 pre, 1 fine infusione, 1 post 2-8 ore
- Visita 8 (week 15): 1 KIT pre
- Visita 9 (week 17): 1 KIT pre
- Visita 10 (week 19): 1 KIT pre
- Visita 11 (week 21): 1 KIT pre
- Visita 13 (week 23): 1 KIT pre
- Visita 15 (week 25): 3 KIT: 1 pre, 1 fine infusione, 1 post 2-8 ore
- Visita 16 (week 27): 1 KIT pre
- Visita 17 (week 29): 1 KIT pre
- Visita 18 (week 31): 1 KIT pre
- Visita 19 (week 33): 1 KIT pre
- Visita 20 (week 35): 1 KIT pre
- Visita 21 (week 37): 3 KIT: 1 pre, 1 fine infusione, 1 post 2-8 ore
- Visita 22 (week 39): 1 KIT pre
- Visita 23 (week 41): 1 KIT pre
- Visita 25 (week 43): 1 KIT pre
- Visita 26 (week 45): 1 KIT pre
- Visita 27 (week 47): 1 KIT pre
- Visita 28 (week 49): 3 KIT: 1 pre, 1 fine infusione, 1 post 2-8 ore
- Visita 29 (week 51): 1 KIT pre
- Visita 30 (week 53): 1 KIT pre
- End of treatment: 1 KIT
- Follow up: 1 KIT



Sempre maggiore complessità in gestione campioni biologici studio correlati:

- Prelievi PK
- Esami centralizzati
- Biopsie mandatorie / opzionali
- Biomarker centralizzati
- Stool sample per microbioma
- PBMC



.... IN CORSA CONTRO IL TEMPO



January 13, 2020

Independent academic clinical research is indispensable for treatment access, and ensuring the most efficient use of resources. Over the decades now, initiating investigators have tackled the challenges of innovative research and the level of regulation and bureaucracy. Much of this burden has resulted from the implementation of regulations which aimed to ensure patient protection and research

Page 1 of 2



Bureaucracy is strangling clinical research

Legislation has not appreciably changed since 2001, but those administering it or working within it are producing more and more bureaucratic demands

Simon Rule *professor of haematology*¹, Steven LeGouill *professor of haematology*²

Joint statement by medical societies and patient advocates

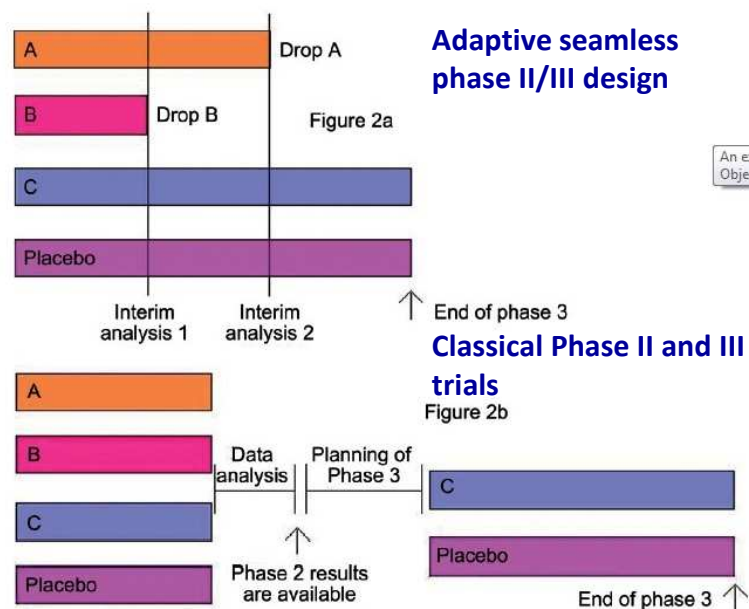


Maggiore complessità dei disegni sperimentali

Adaptive clinical trials in oncology

Donald A. Berry

Berry D, et al. *Stat Med*. 2010;29(18):3616-3634. doi:10.1002/sim.4047



Adaptive seamless phase II/III design (2a) and its comparison with classical Phase II and III trials (2b)

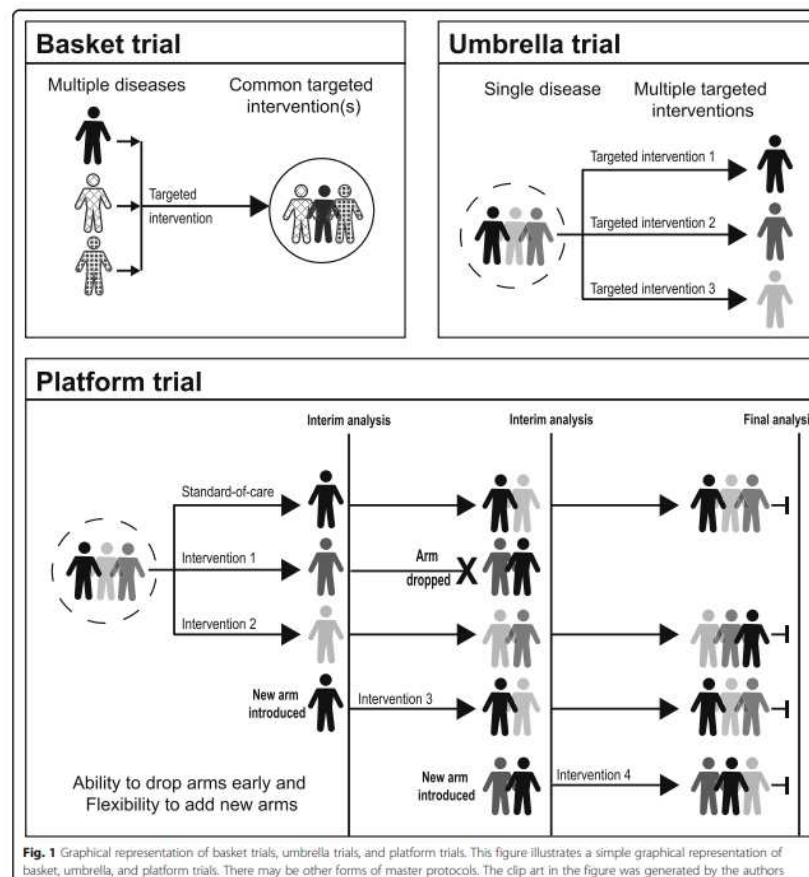


Fig. 1 Graphical representation of basket trials, umbrella trials, and platform trials. This figure illustrates a simple graphical representation of basket, umbrella, and platform trials. There may be other forms of master protocols. The clip art in the figure was generated by the authors

Attività da remoto nella gestione delle Sperimentazioni Cliniche

Therapeutic Innovation & Regulatory Science

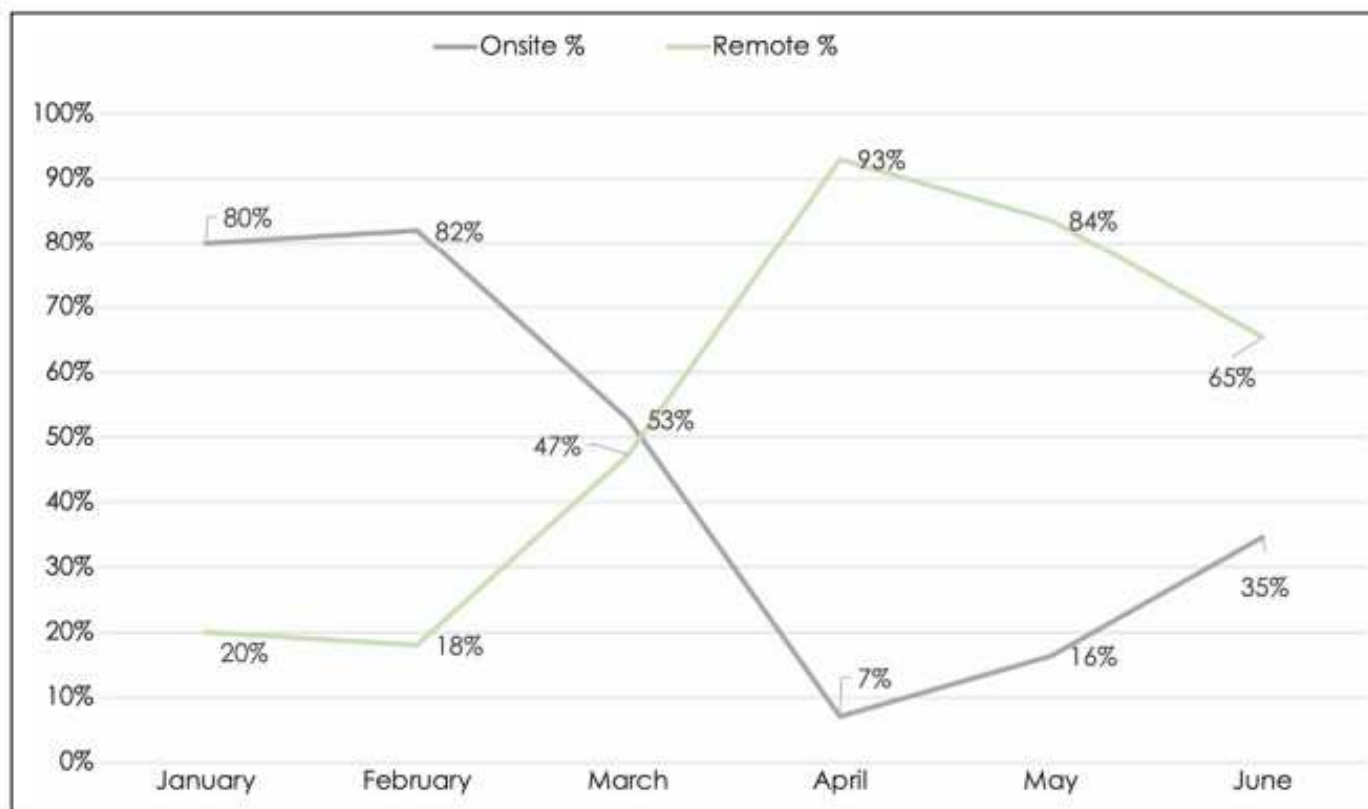


Fig. 3 Increased Remote Monitoring Visits and RBM in Response to the COVID-19 Pandemic. Graph shows data from 1 of 3 companies providing monitoring visit data (n = ~ 1,200 trials), but trends were similar across all 3 companies.

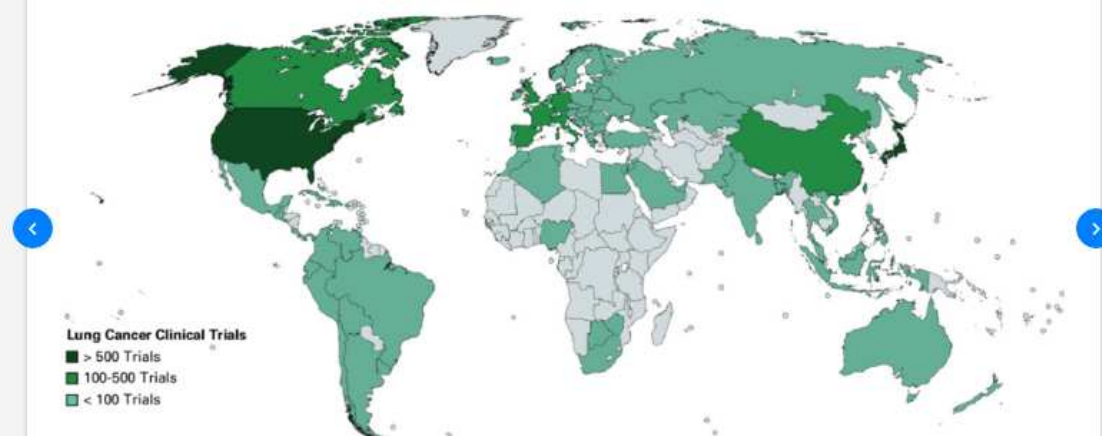
Ther Innov Regul Sci, 2021 Apr 29;1-8.

Fig 2- available via license: [Creative Commons Attribution 4.0 International](#)

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View publication



Geographic distribution of clinical trials for lung cancer.

Sperimentazioni per anno: confronto Unione Europea – Italia (quinquennio)

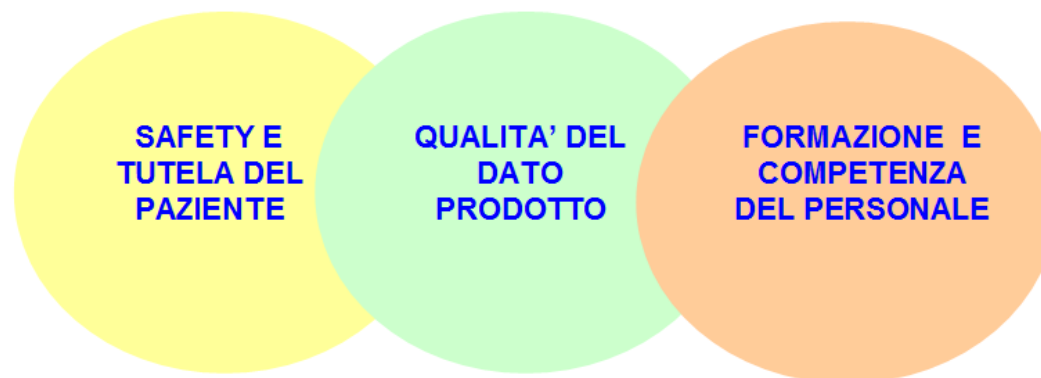
Anno	SC in UE *	SC presentate in Italia **	% Italia / UE	SC autorizzate in Italia ***	% Italia / UE
2014	3.249	723	22,3	592	18,2
2015	3.918	744	19,0	672	17,2
2016	3.255	767	23,6	660	20,3
2017	3.125	669	21,4	564	18,0
2018	3.256	716	22,0	666	20,5

* Numero di studi caricati nel sistema europeo

** Il numero di sperimentazioni cliniche presentate in Italia nel 2018 è tratto dalla Tabella 5 mentre per gli altri anni è tratto dalle edizioni precedenti di questo Rapporto Nazionale

*** Il numero di sperimentazioni cliniche autorizzate in Italia è tratto dalla Tabella 4

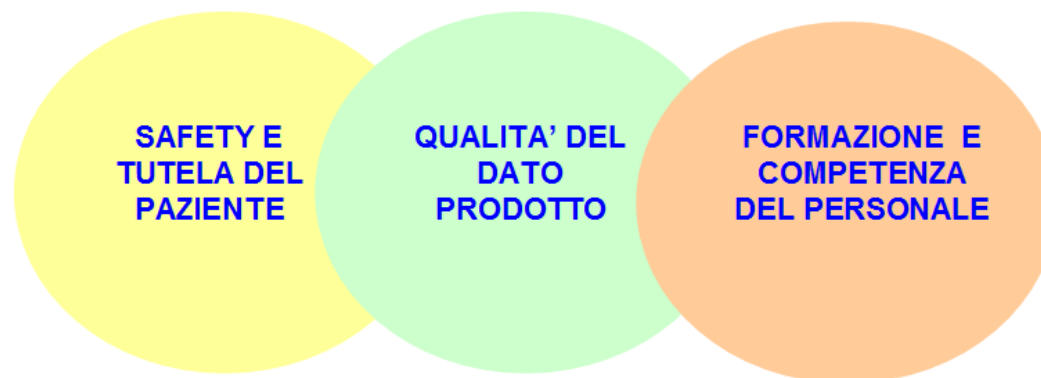
QUALITA' DEI CENTRI CLINICI SPERIMENTALI



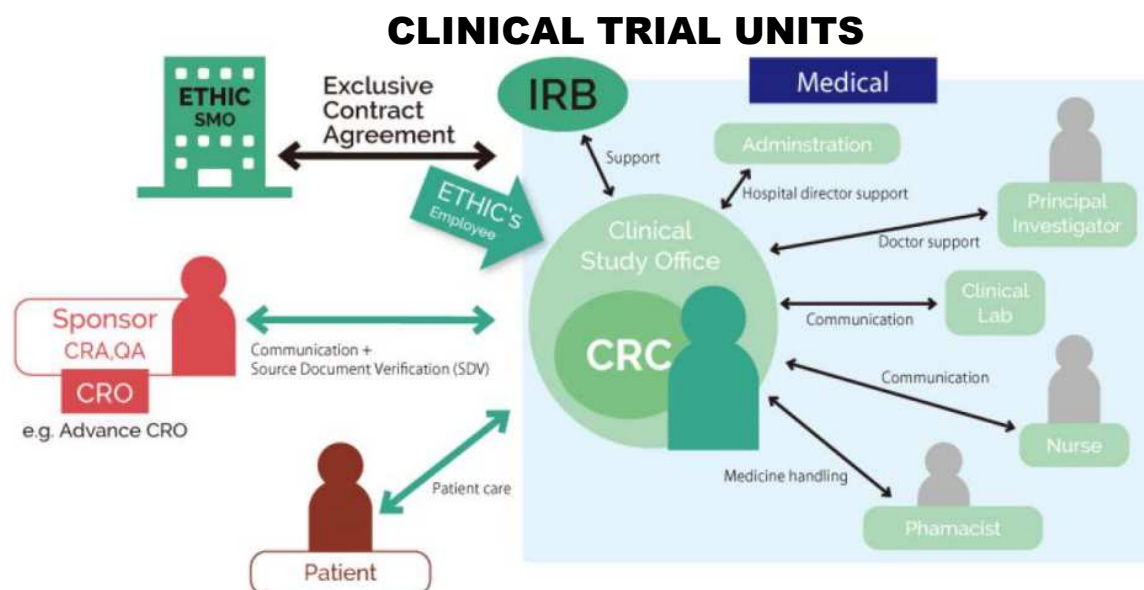
**INVESTIRE SULLA
FORMAZIONE DEL
PERSONALE CON PIANI
DI FORMAZIONE
SPECIFICI**

- o Prevedere piano formativo annuale
- o Proporzionalità formazione GCP in base al ruolo ricoperto in termini di frequenza ad argomenti trattati
- o Formazione sulla gestione delle emergenza (es. BLSD, ALS etc)
- o Formazione ad hoc in base al ruolo ricoperto sullo staff di studio (es. CRC, infermiere di ricerca, investigator etc.)

QUALITA' DEI CENTRI CLINICI SPERIMENTALI



**CREAZIONE DI
STRUTTURE
DEDICATE ALLA
RICERCA CLINICA
(& PERSONALE
DEDICATO)**



Creazione di Clinical Trial Unit

Clinical Cancer Research

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Cancer Therapy: Clinical

Modifying the Clinical Research Infrastructure at a Dedicated Clinical Trials Unit: Assessment of Trial Development, Activation, and Participant Accrual

Chad Tang, Kenneth R. Hess, Dwana Sanders, Suzanne E. Davis, Aman U. Buzdar, Razelle Kurzrock, J. Jack Lee, Funda Meric-Bernstam, and David S. Hong

DOI: 10.1158/1078-0432.CCR-16-1936 Published March 2017 

How a Clinical Trial Unit can improve independent clinical research in rare tumors: the Italian Sarcoma Group experience

Emanuela Marchesi , Celeste Cagnazzo, Irene Quattrini, Martina Piccinni Leopardi, Chiara Villa, Giovanni Grignani, Lorenzo D'Ambrosio, Silvia Stacchiotti, Paolo Giovanni Casali and Piero Picci

Clinical Sarcoma Research 2017 7:4

<https://doi.org/10.1186/s13569-017-0068-4> | © The Author(s) 2017

Received: 9 December 2016 | Accepted: 7 February 2017 | Published: 28 February 2017

The role of Clinical Trial Units in investigator- and industry-initiated research projects

Belinda von Niederhäusern, Christiane Pauli-Magnus, Thomas Fabbro

DOI: <https://doi.org/10.4414/smw.2015.14161>

Publication Date: 02.07.2015

Swiss Med Wkly. 2015;145:w14161

IMPLEMENTARE UN MODELLO ORGANIZZATIVO PER LA RICERCA CLINICA:

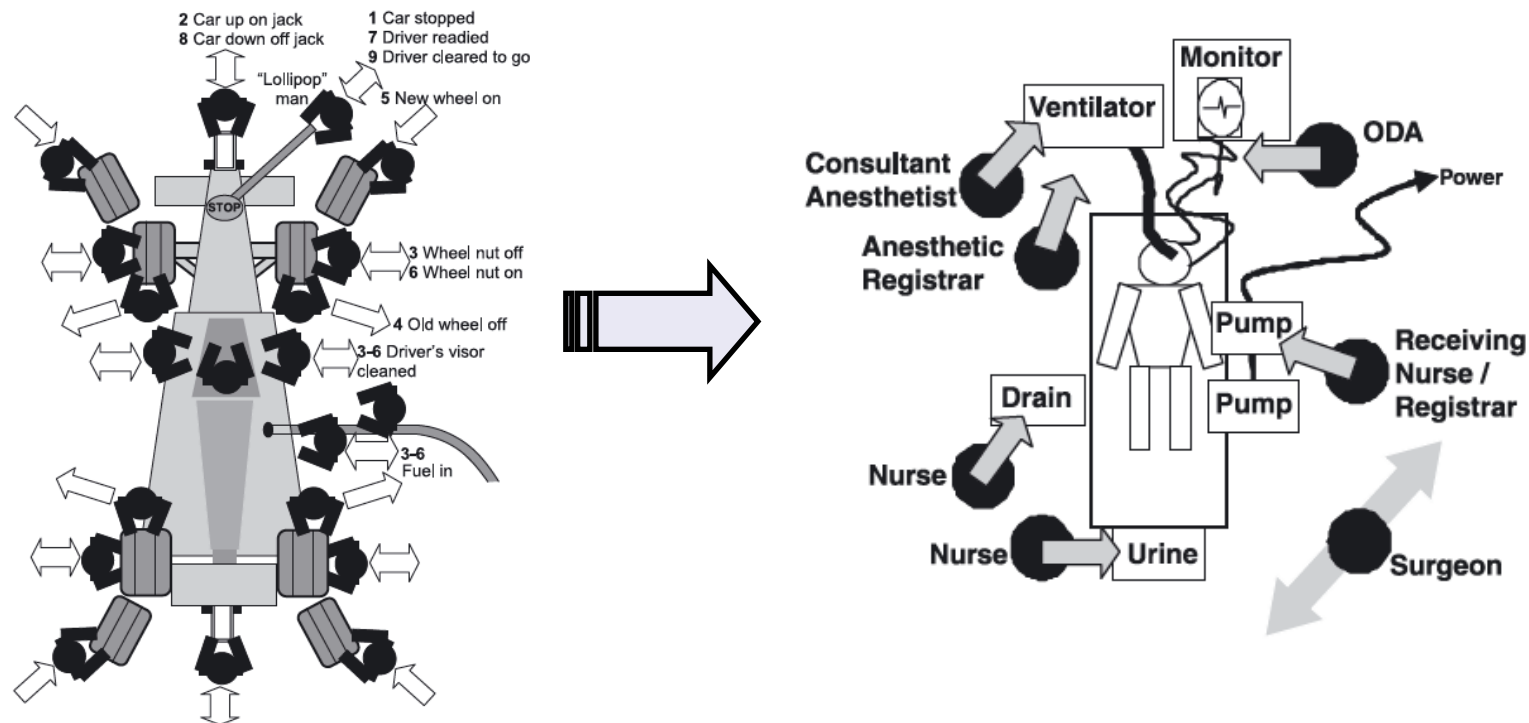
- creazione CTU
- investire sulle figure professionali (personale dedicato alla ricerca)
- valorizzare le multidisciplinarietà
- creazione di un Sistema di Gestione Qualità → standardizzare procedure e processi
- piano formativo annuale dedicato alle sperimentazioni cliniche

- OTTIMIZZARE IL PROPRIO MODELLO ORGANIZZATIVO
- IMPLEMENTARE SICUREZZA E QUALITA' DELLE PRESTAZIONI

Patient handover from surgery to intensive care: using Formula 1 pit-stop and aviation models to improve safety and quality

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ANGUS MCEWAN FRCA‡, NICK PIGOTT FRCPCH§, MARTIN
J. ELLIOTT MD, FRCS¶, ANNETTE MCQUILLAN BSc†,
CAROL MACDONALD BSc† AND ALLAN J. GOLDMAN§

*Nuffield Department of Surgery, University of Oxford, Oxford, †Great Ormond Street Hospital
for Children NHS Trust, London, ‡Department of Anaesthesia, Great Ormond Street Hospital
for Children NHS Trust, London, §Cardiac Critical Care, Great Ormond Street Hospital for
Children, London, ¶Cardiothoracic Surgery, Great Ormond Street Hospital for Children NHS
Trust, London, UK

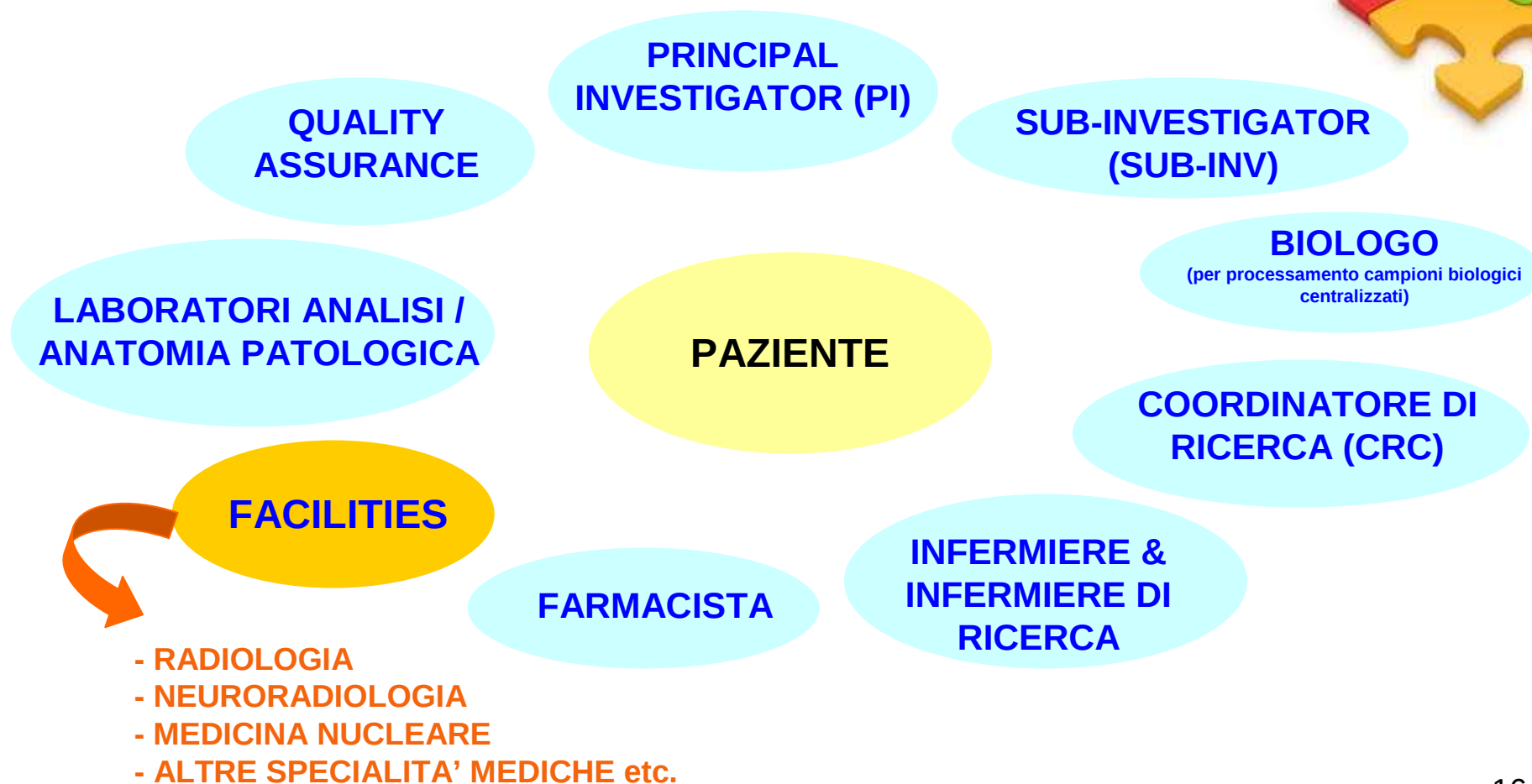


Capacità di coordinamento e teamwork tra centro clinico e attori esterni



ATTORI DAL LATO DEL CENTRO CLINICO

Lavoro in team in un ambiente multidisciplinare



PRINCIPAL INVESTIGATOR (PI)



Alcune mansioni del PI:

- Discussione e acquisizione Consenso Informato
- Prescrizione farmaco sperimentale
- Valutazione AE/SAE
- Aggiornamento/mantenimento della documentazione di studio
- Corretta conservazione della documentazione di studio
- Corretta conservazione del farmaco sperimentale
- Conduzione dello studio secondo le specifiche del protocollo e secondo le ICH-GCP
- Firma delle CRF
- Training dello staff da lui delegato
- Oversight su tutto lo staff da lui delegato

Etc. Etc. Etc.



Il PI può delegare parte delle sue mansioni ai componenti del suo staff



PRINCIPAL INVESTIGATOR



DELEGATION LOG:

DELEGA DELLE TASK DAL PI ALLO STAFF DI STUDIO

Study Task Key:

- | | | |
|---|--|--|
| 1. Manage IRB/EC communications & submissions
2. Maintain essential documents
3. Receive/access safety notifications
4. Screen/recruit study subjects
5. Obtain informed consent
6. Perform physical exam
7. Obtain medical/medication history
8. Confirm eligibility criteria (inclusion/exclusion)
9. Perform basic assessments (e.g. vital signs, weight, ECG)
10. Make study related medical decisions | 11. Evaluate study related test results
12. Assess AE/SAE causality
13. Report SAEs
14. Collect (a)/ process (b) and/or ship biological samples (c)
15. Make (e)CRF entries, corrections and queries
16. Sign off on (e)CRF visit data
17. Use IWRS/IVRS
18. Manage IP receipt, storage, & temperature monitor
19. Prepare and dispense IP
20. Performs IP accountability | 21. Administer IP
22. Other * Scan submission to vendor
23. Other * Perform XRAY/images
24. Other * Manage eCOA devices
25. Other * <input type="text"/>
26. Other * <input type="text"/>
27. Other * <input type="text"/>
28. Other * <input type="text"/>
29. Other * <input type="text"/>
30. Other * <input type="text"/> |
|---|--|--|

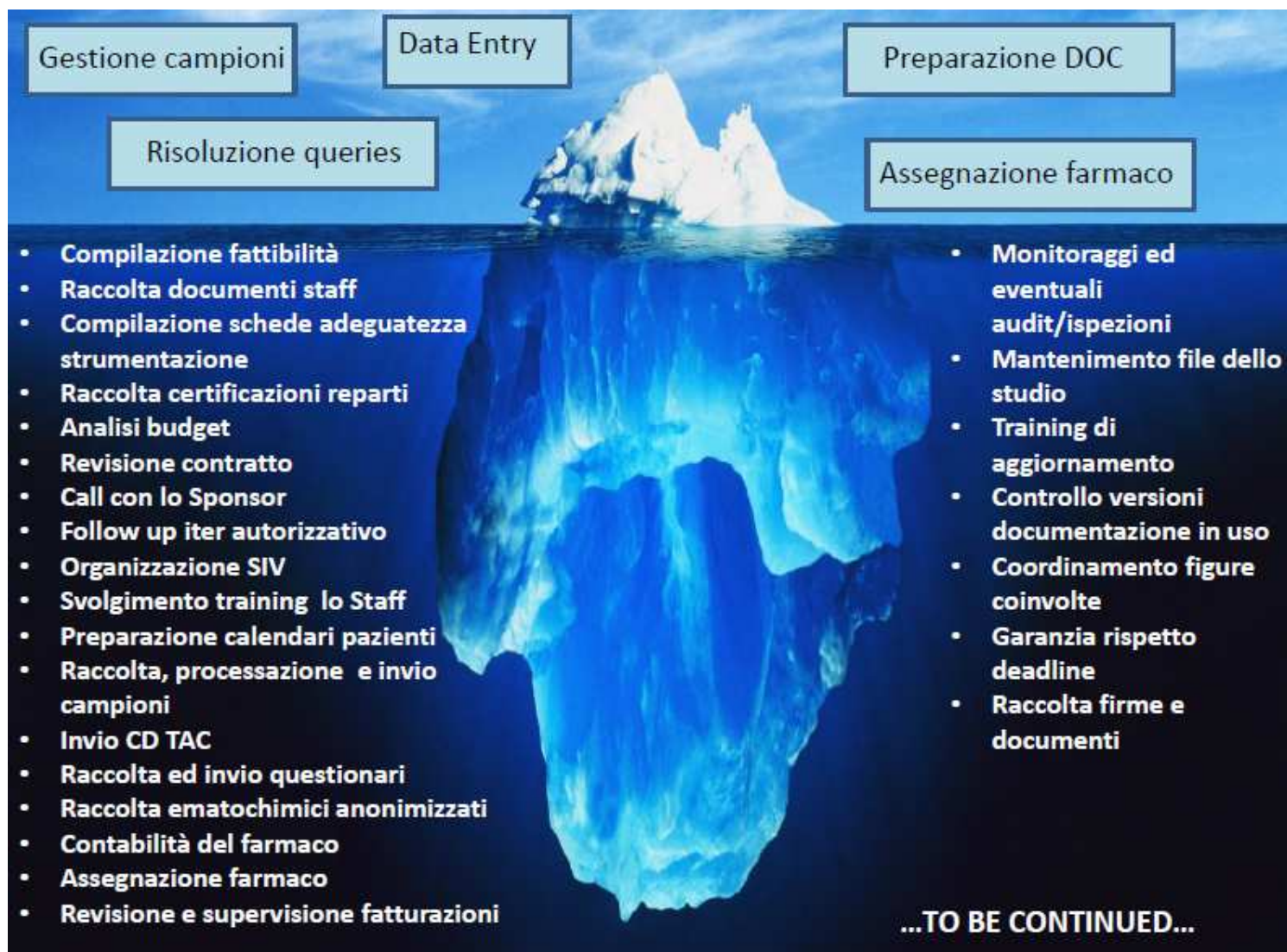
(*) Other tasks may be those that are study specific or are local regulatory requirements and have been identified by the Study Sponsor.

(**) Necessary training for task must be completed prior to performing a study task.

(***) PI initials and delegation start date indicate date when delegation is authorized by PI. This date should not be after "start of task(s)" date.

Name	Signature My signature below indicates that I accept the study task.	Initials	Study Role	Study Task(s) (Select from key)	PI initials and delegation start date *** (dd/mmm/yyyy)	Start of task(s)** (dd/mmm/yyyy)	End of task(s) (dd/mmm/yyyy)	PI initials and delegation end date (dd/mmm/yyyy)
MARIO ROSSI	<i>Mario Rossi</i>	MR	SUB-INVESTIGATOR	3,4,5,6,7,8,9,10,11,12,13,19	01.02.2020 ROSSO	01.02.2020		
LUIGI VERDI	<i>Luigi Verdi</i>	LV	STUDY COORDINATOR	1,2,17,18,20	01.02.2020 ROSSO	01.02.2020		
MARIA BIANCHI	<i>Maria Bianchi</i>	MB	STUDY NURSE	9,12,14,21	01.02.2020 ROSSO	01.02.2020		
ANGELO NERI	<i>Angelo Neri</i>	AN	PHARMACIST	18,19,20	01.02.2020 ROSSO	01.02.2020		

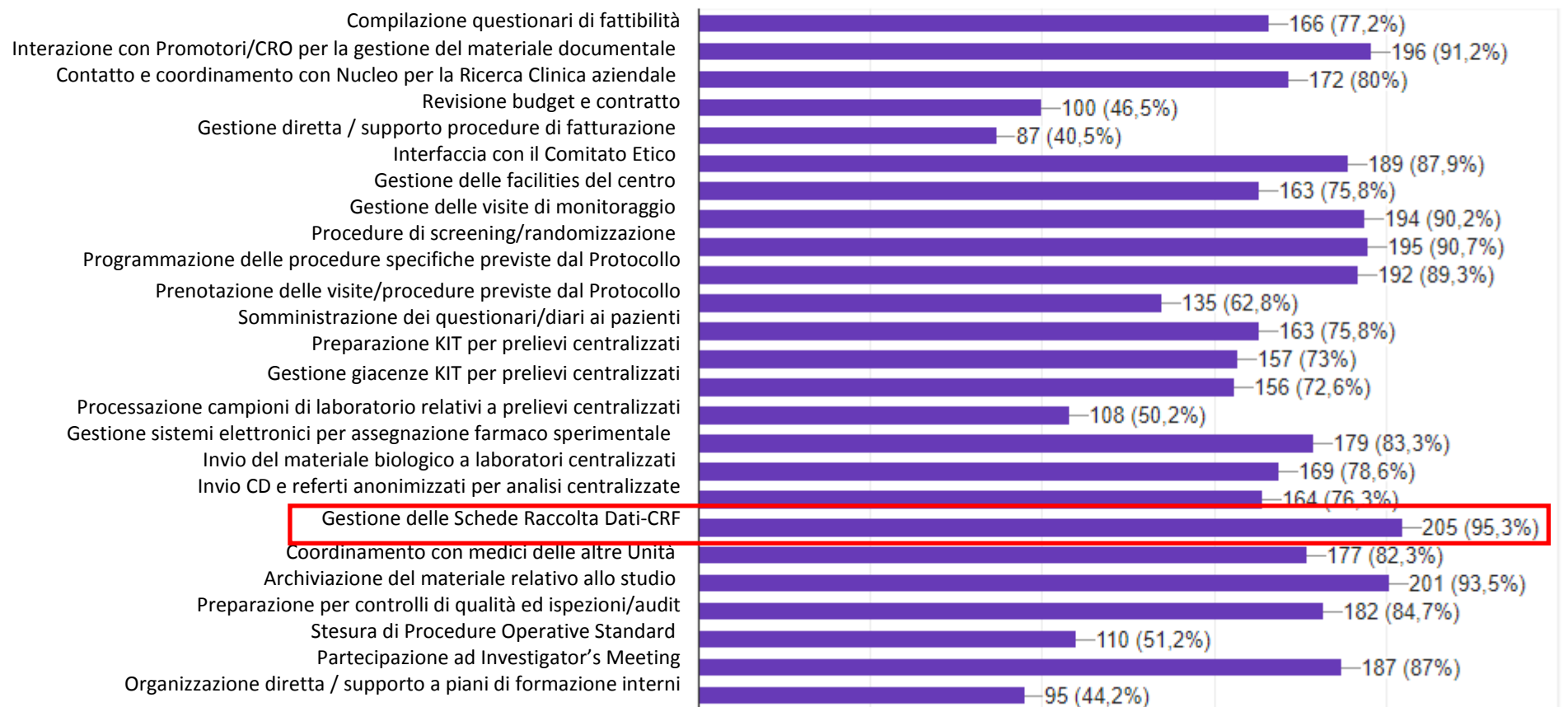
COORDINATORE DI RICERCA CLINICA (o *STUDY COORDINATOR*)



Un datore di lavoro - una job description

Quali tra le seguenti attività svolgi?

215 risposte



INFERMIERE DI RICERCA

Infermiere impiegato principalmente per effettuare ricerca all'interno di contesti clinici e con documentata formazione in GCP.

Alcune delle funzioni svolte dall'infermiere di ricerca includono:

- riportare eventi avversi;
- coordinare gli appuntamenti e i trattamenti dei pazienti in studio;
- comunicare con il team di ricerca e coi pazienti;
- effettuare valutazioni dei pazienti sia di routine che specifiche per la ricerca (es. parametri vitali);
- prelievo dei campioni biologici (es. prelievi ematici);
- contribuire alla stesura dei rapporti di ricerca se ve ne sia la necessità;
- compilazione del diario infermieristico;
- somministrazione delle terapie sperimentali;
- partecipazione a SIV e monitoraggi;

Etc. Etc.



Coordinamento multidisciplinare sulle attività di studio

Table 7-5 ECG collection plan for approximately 30 enrolled patients at selected sites

Cycle	Day	Time	ECG Type	Number of ECGs
Screening		Anytime	12 Lead	3
1	1	Pre-dose Post-dose 1 h (within 15 min prior to PK) Post-dose 2 h (within 15 min prior to PK) Post-dose 4 h (within 15 min prior to PK) Post-dose 8 h (within 15 min prior to PK)	12 Lead	3
1	15	Pre-dose Post-dose 1 h (within 15 min prior to PK) Post-dose 2 h (within 15 min prior to PK) Post-dose 4 h (within 15 min prior to PK) Post-dose 8 h (within 15 min prior to PK)	12 Lead	3
3	1	Pre-dose (within 15 min prior to PK)	12 Lead	3
EOT		Anytime	12 Lead	3
Unscheduled ECG		Anytime if clinically indicated	12 Lead	3



Table 7-7 Pharmacokinetic blood collection log for approximately 30 enrolled patients at selected sites

Cycle	Day	Scheduled Time Point	Dose Reference ID	PK Sample No	Sample Volume (mL)
1	1	Pre-dose/0h	1	1	3
1	1	Post-dose 0.5h ($\pm$ 5min)	1	2	3
1	1	Post-dose 1h ($\pm$ 10min)	1	3	3
1	1	Post-dose 2h ($\pm$ 10min)	1	4	3
1	1	Post-dose 4h ($\pm$ 20min)	1	5	3
1	1	Post-dose 6h ($\pm$ 20min)	1	6	3
1	1	Post-dose 8h ($\pm$ 20min)	1	7	3
1	15	Pre-dose/0h	2	201 ^a	3
1	15	Post-dose 0.5h ($\pm$ 5min)	2	9	3
1	15	Post-dose 1h ($\pm$ 10min)	2	10	3
1	15	Post-dose 2h ($\pm$ 10min)	2	11	3
1	15	Post-dose 4h ($\pm$ 20min)	2	12	3
1	15	Post-dose 6h ($\pm$ 20min)	2	13	3
1	15	Post-dose 8h ($\pm$ 20min)	2	14	3
3	1	Pre-dose/0h	3	301 ^a	3
Unscheduled	Anytime			1001+	3
Total scheduled					45

^aDose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample



Coordinamento multidisciplinare sulle attività di studio

Table 7-5 ECG collection plan for approximately 30 enrolled patients at selected sites

Cycle	Day	Time	ECG Type	Number of ECGs
Screening		Anytime	12 Lead	3
1	1	Pre-dose Post-dose 1 h (within 15 min prior to PK) Post-dose 2 h (within 15 min prior to PK) Post-dose 4 h (within 15 min prior to PK) Post-dose 8 h (within 15 min prior to PK)	12 Lead	3
1	15	Pre-dose Post-dose 1 h (within 15 min prior to PK) Post-dose 2 h (within 15 min prior to PK) Post-dose 4 h (within 15 min prior to PK) Post-dose 8 h (within 15 min prior to PK)	12 Lead	3
3	1	Pre-dose (within 15 min prior to PK)	12 Lead	3
EOT		Anytime	12 Lead	3
Unscheduled ECG		Anytime if clinically indicated	12 Lead	3

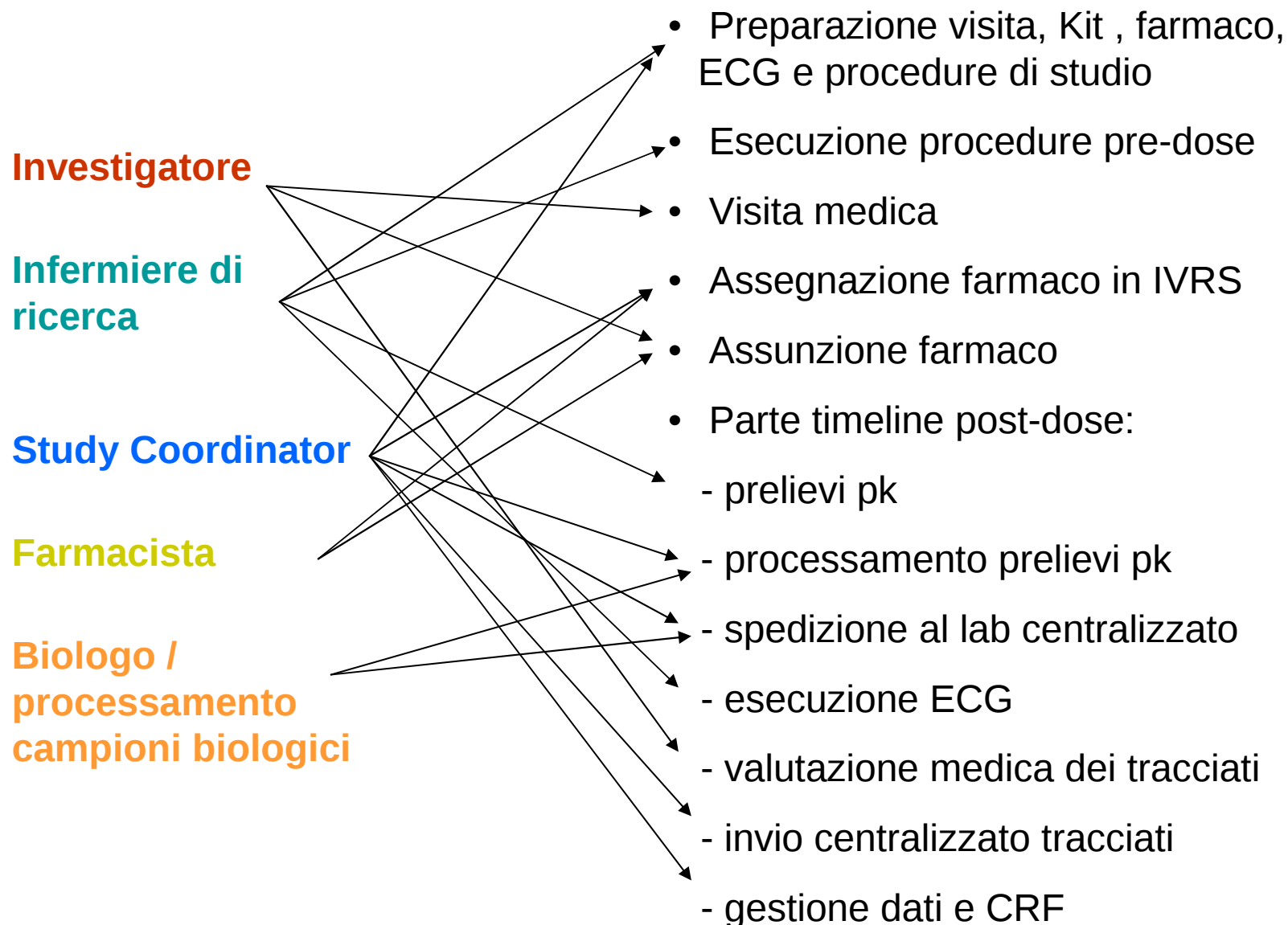
Table 7-7 Pharmacokinetic blood collection log for approximately 30 enrolled patients at selected sites

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1	1	Post-dose 1h ($\pm$ 10min)	1	3	3
1	1	Post-dose 2h ($\pm$ 10min)	1	4	3
1	1	Post-dose 4h ($\pm$ 20min)	1	5	3
1	1	Post-dose 6h ($\pm$ 20min)	1	6	3
1	1	Post-dose 8h ($\pm$ 20min)	1	7	3
1	15	Pre-dose/0h	2	201 ^a	3
1	15	Post-dose 0.5h ($\pm$ 5min)	2	9	3
1	15	Post-dose 1h ($\pm$ 10min)	2	10	3
1	15	Post-dose 2h ($\pm$ 10min)	2	11	3
1	15	Post-dose 4h ($\pm$ 20min)	2	12	3
1	15	Post-dose 6h ($\pm$ 20min)	2	13	3
1	15	Post-dose 8h ($\pm$ 20min)	2	14	3
3	1	Pre-dose/0h	3	301 ^a	3
Unscheduled	Anytime			1001+	3
Total scheduled					45

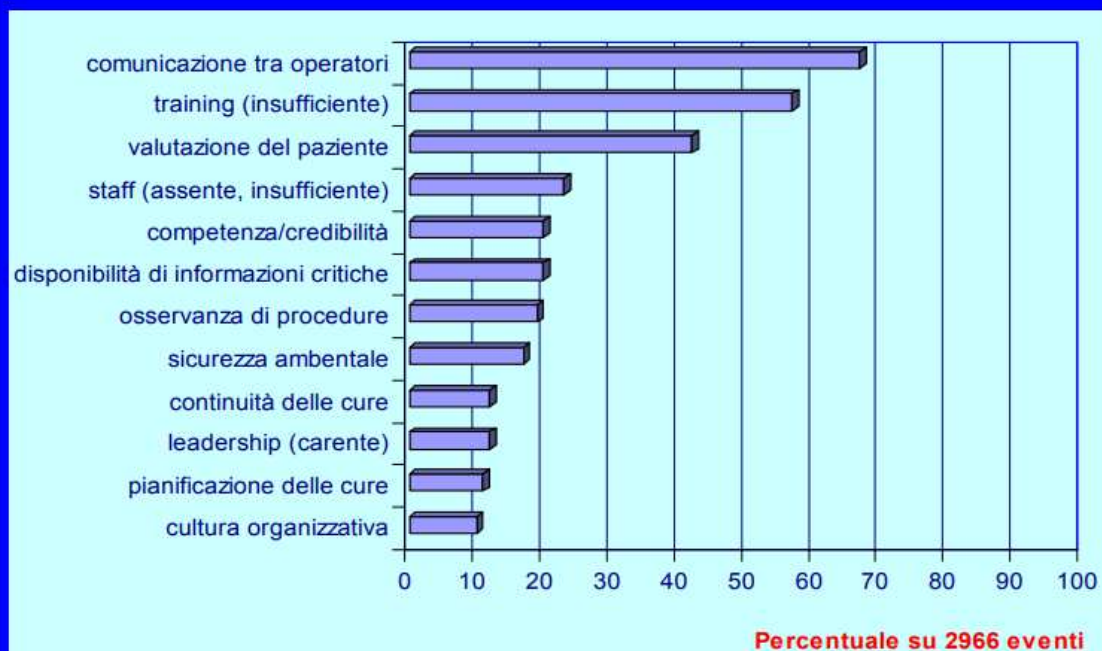
^aDose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample

- Preparazione visita, Kit , farmaco, ECG e procedure di studio
- Esecuzione procedure pre-dose
- Visita medica
- Assegnazione farmaco in IVRS
- Assunzione farmaco
- Parte timeline post-dose:
 - prelievi pk
 - processamento prelievi pk
 - spedizione al lab centralizzato
 - esecuzione ECG
 - valutazione medica dei tracciati
 - invio centralizzato tracciati
 - gestione dati e CRF

Coordinamento multidisciplinare sulle attività di studio



JCHAO: RCA di eventi sentinella (1995-2004)



COMUNICAZIONE TRA OPERATORI



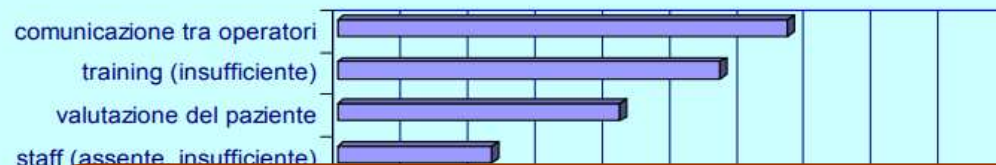
C. Consolante (Agenzia di Sanità Pubblica del Lazio) - Corso "Il Rischio Clinico", Napoli 11 dicembre 2006



Errore umano e debolezza di sistema:

- Nel 72.4 % gli incidenti sono la conseguenza di problemi organizzativi
- Nel 27.6 % sono legati a negligenza, imperizia, imprudenza.

Harvard Medical Practice Study(1991)



ANALYSIS OF DEVIATIONS AND NON-CONFORMITIES IN A PHASE 1 UNIT: THE EXPERIENCE OF NIGUARDA CANCER CENTER.

Overall 349 minor D/NCs were identified between 2019 and 2020 (average 19,4 per study) and 17 majors findings (average 0.94 per study). No critical findings were found.

Organizations factors highly influences all findings, even if human factors are strongly involved too, especially in informed consent procedure and drugs management findings.

Lack of communication was the main cause of D/NCs and it ranks in the 3th quarter of influence for minor and in the 2nd quarter for major deviations.

- Nel 27.6 % sono legati a negligenza, imperizia, imprudenza.

Harvard Medical Practice Study(1991)





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stefano.stabile@ospedaleniguarda.it

<https://it.linkedin.com/in/stefano-stabile-ba98ba44>

Contatti GIDM:

Per informazioni di carattere generale segreteria@gidm.org

Per questioni relative all'iscrizione al Gruppo o rinnovo statu associativo iscrizione@gidm.org

Per questioni relative alla sezione BACHECA e/o offerte di lavoro job.segreteria@gidm.org

Per contattare direttamente il referente Formazione del GIDM formazione@gidm.org

Per contattare direttamente il Presidente del GIDM presidente@gidm.org

www.gidm.org

<https://it.linkedin.com/in/gidm-coordinatori-di-ricerca-clinica-777260167>