Il COVID quale Catalizzatore della Collaborazione Interdisciplinare con Approcci Innovativi nella Ricerca

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«I can’t imagine we’ll go back to doing clinical research in the future the way we did in the past»

Francis S. Collins, MD, PhD, Director, National Institutes of Health

COVID Research
A magnifying glass on existing problems

Significant duplication and imbalance of topics

- Trial ‘hype’ on chloroquine / hydroxychloroquine
- Significant redundancies also in other fields
- Almost no trials on non-drug interventions

Significant number of methodologically flawed studies

- Many poorly designed trials (i.e. no control group, no randomisation)
- Most studies too small to be informative
- Wide variation in outcome measures

Significant increase in early access study results

- Many poorly reported studies
- Often disagreement between text and tables
- Irresponsible dissemination of flawed studies

Glasziou PP and Sanders S: Waste in Covid-19 research. BMJ 2020

Esempio di ricerca collaborativa interdisciplinare con approccio innovativo

A data-driven approach to identify risk profiles and protective drugs in COVID-19

Pietro E. Cippà[a,b,1,2], Federica Cugnata[c,1], Paolo Ferrari[a,d,e,1], Chiara Brombin[c], Lorenzo Ruinelli[f], Giorgia Bianchi[a], Nicola Beria[a], Lukas Schulz[a], Enos Bernasconi[d,g,h], Paolo Merlani[h,i], Alessandro Ceschi[b,d,j,k,1], and Clelia Di Serio[c,d,1,2]

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Proc Natl Acad Sci U S A . 2021 Jan 7;118(1):e2016877118

- Interdisciplinarità: team centrale di studio composto da 3 clinici e da 3 biostatistici
- Collaboratività: impostazione delle domande di fondo e della metodologia di studio in modo concordato e condiviso - Incontri (remoto) regolari e intense discussioni

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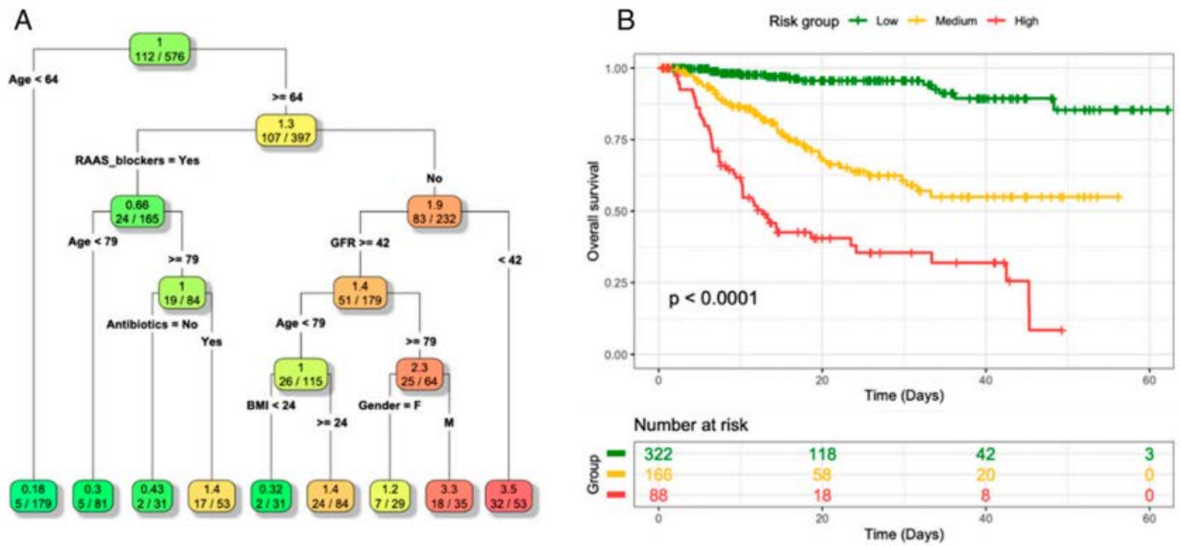
- Approcci innovativi: analisi biostatistiche avanzate e in parte sperimentali per ovviare alle limitazioni derivanti da dati in parte frammentati e con bias insiti nella raccolta nel contesto emergenziale

Esempio di ricerca collaborativa interdisciplinare con approccio innovativo

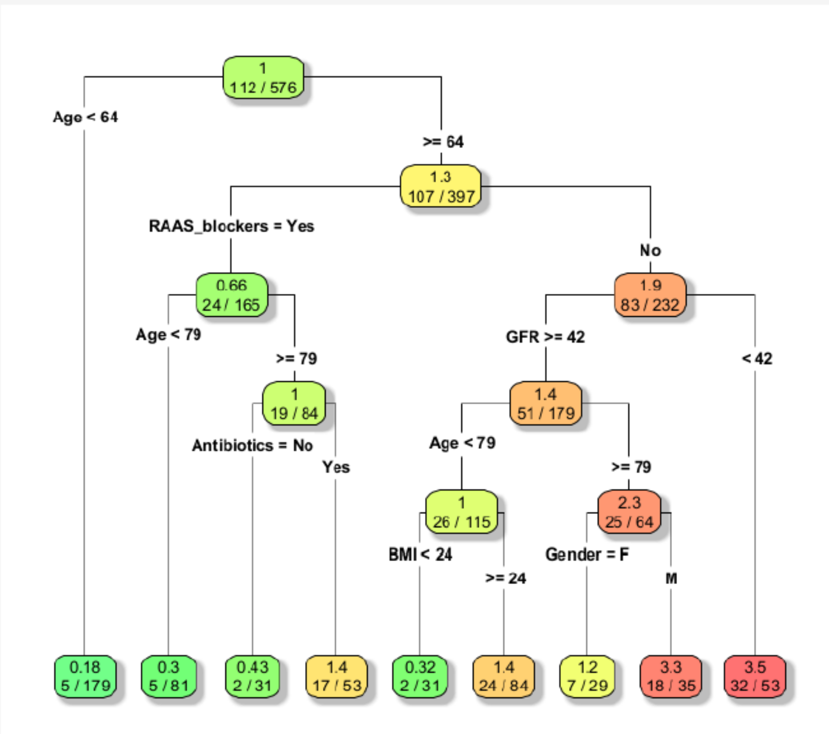
- Approccio data-driven con applicazione di:
  - ✓ alberi di sopravvivenza (ST) per definire una stratificazione multistrato di rischio (multilayer risk stratification) e per determinare l’effetto dei farmaci sulla sopravvivenza dei pazienti
  - ✓ reti Bayesiane per analizzare le interdipendenze complesse, inclusi effetti confondenti, tra fattori di rischi e impatto delle terapie sulla sopravvivenza



Esempio di ricerca collaborativa interdisciplinare con approccio innovativo

- Survival tree analysis:

Demographic, anthropometric and clinical characteristics, comorbidities, pneumonia, and drug therapy were entered in the model as covariates



To limit overfitting while having enough observations in the nodes to properly carry out further analyses, in the tree building phase, the minimum number of observations in any terminal node was set equal to 20.

High risk

- Age $\geq$ 63.5 & RAASi=no &eGFR $<$ 41.5
- Age $\geq$ 78.5 & RAASi=no & & eGFR $\geq$ 41.5 &Gender=Male

Medium risk

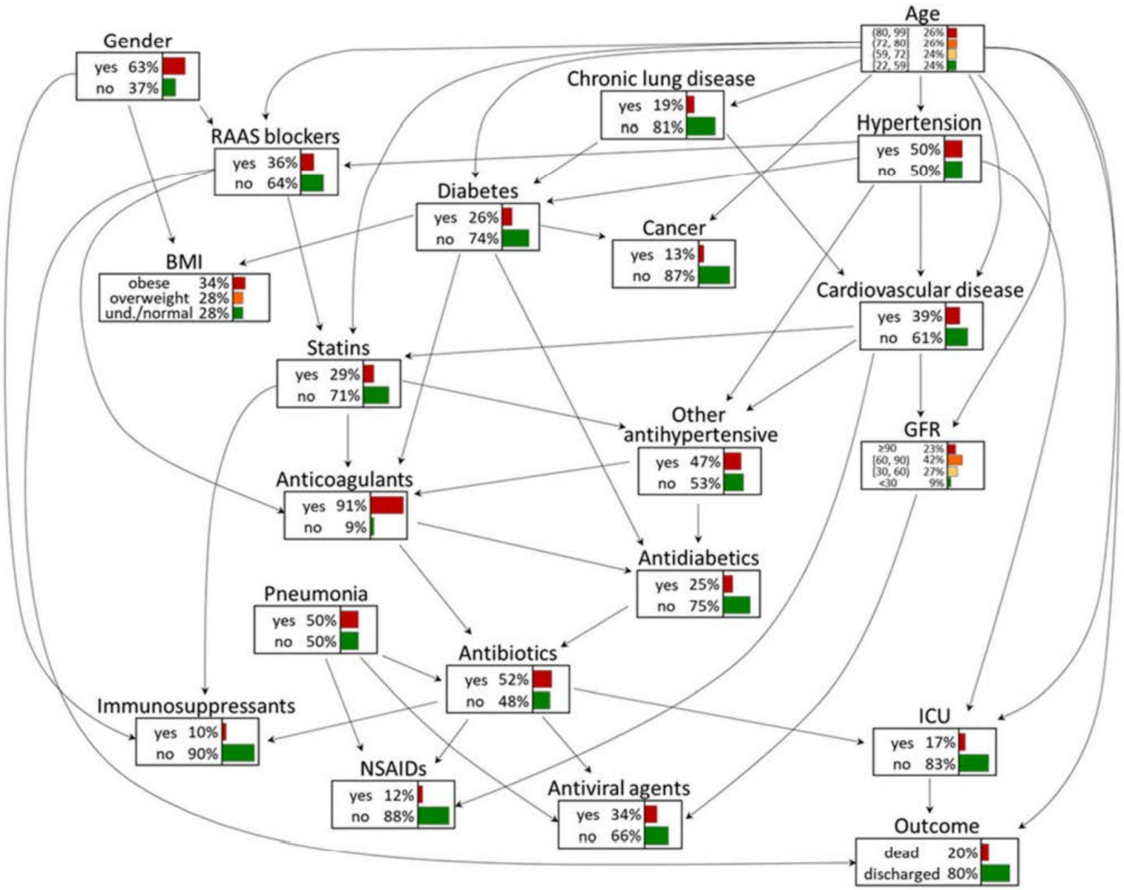
- Age between 63.5 and 78.5 & RAASi=no & eGFR $\geq$ 41.5 & BMI $\geq$ 24 .24
- Age $\geq$ 78.5 & RAASi=no & & eGFR $\geq$ 41.5 &Gender=Female
- Age $\geq$ 78.5 & RAASi=yes & antibiotics=yes

Low risk

- Age< 63.5
- Age between 63.5 and 78.5 & RAASi =yes
- Age between 63.5 and 78.5 & RAASi=no & gfr $\geq$ 41.5 & BMI $<$ 24.24
- Age $\geq$ 78.5 & RAASi=yes & Antibiotics=no

Esempio di ricerca collaborativa interdisciplinare con approccio innovativo

- Bayesian network (permettono di studiare scenari ipotetici: una volta che la rete è stata impostata, fissando i valori di alcuni «nodi» è possibile studiare come la modifica di una certa variabile si propaga attraverso la rete a tutte le altre variabili e alla variabile target):



- ↓ probabilità decesso in ipertesi da 31% a 12% se trattati con RAASi
- Probabilità di decesso in ipertesi trattati con RAASi 10.9% vs 33.2% con altri antiipertensivi

Esempio di ricerca collaborativa interdisciplinare con approccio innovativo

- Risultato principale: tutti gli approcci applicati hanno evidenziato un ruolo benefico e protettivo del trattamento con RAASi nel ridurre il rischio di decesso nei pazienti COVID ospedalizzati
  → studio randomizzato controllato

Esempio di ricerca collaborativa interdisciplinare con approccio innovativo

- Lezioni apprese:
  - ✓ Dal punto di vista clinico, un farmaco di uso comune, sicuro e a basso prezzo ha dimostrato un effetto rilevante
  - ✓ Dal punto di vista biostatistico
    - sottolineato ruolo essenziale della raccolta sistematica, qualitativamente valida, dei dati e della condivisione degli stessi
    - evidenziato ruolo di tecniche biostatistiche avanzate e innovative «data-driven» nel chiarire relazioni complesse tipiche di fenomeni e malattie complesse

→ **Centralità del lavoro collaborativo in team interdisciplinare**

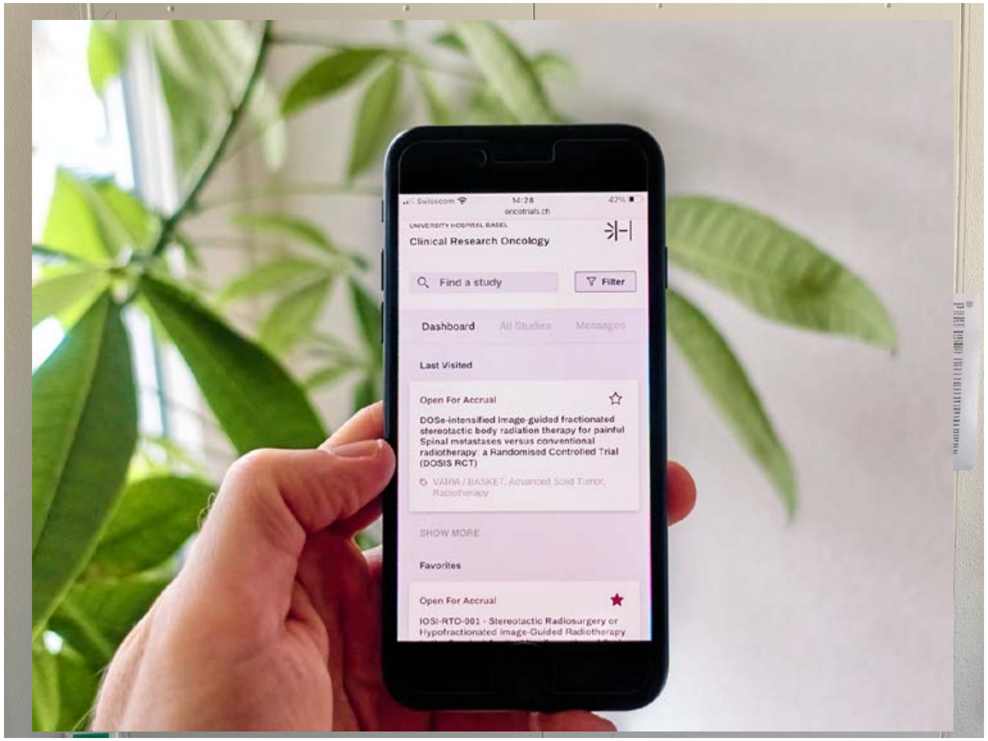
Altri ingredienti di una ricerca clinica rilevante per i pazienti

- Problem base and priority setting
- Context placement and information gain
- Real life circumstances
- Patient centeredness
- Feasibility
- Transparency

Ioannidis JP: What makes clinical research useful? Plos Medicine 2016

Sfuttare il potenziale dei dati e della digitalizzazione

- Per connettere i team di ricerca e i partecipanti
- Per una gestione e supporto efficace degli studi clinici
- Per facilitare i processi della ricerca



Passi concreti in Svizzera

- Comunicato stampa congiunto di Swissmedic e swissethics il 1.11.2021 sugli studi clinici decentralizzati (DCTs) con medicamenti:

swissmedic swissethics

Decentralised clinical trials (DCTs) with medicinal products in Switzerland

(Version 1.1, 25 October 2021)

Altri tipi (disegni) di studi clinici che possibilmente subiranno un'accelerazione «post-COVID»

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

REVIEW

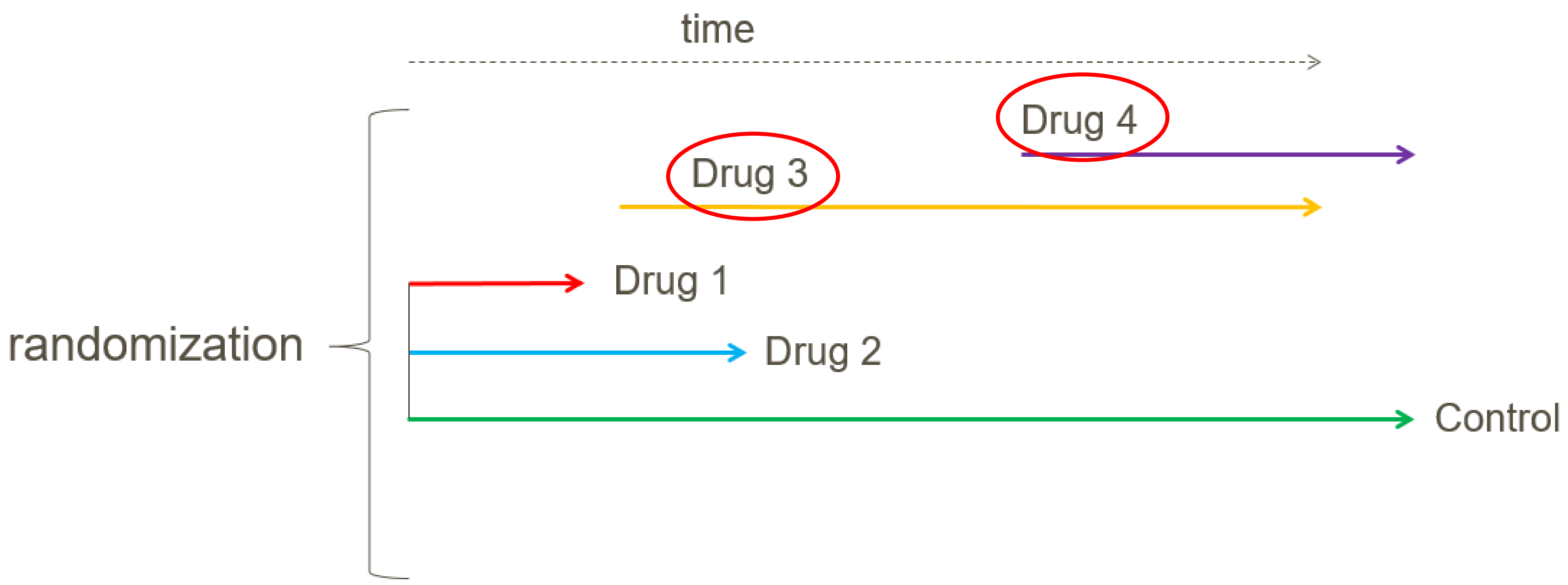
Collaborative Platform Trials to Fight COVID-19: Methodological and Regulatory Considerations for a Better Societal Outcome

Olivier Collignon[1,*], Carl-Fredrik Burman[2], Martin Posch[3] and Anja Schiel[4]

Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Altri tipi (disegni) di studi clinici che possibilmente subiranno un'accelerazione «post-COVID»

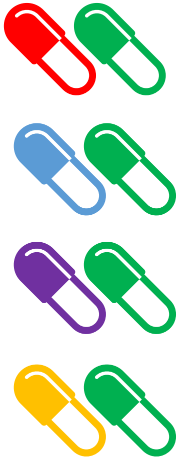
- Platform trials sono "designs" innovati e complessi



Altri tipi (disegni) di studi clinici che possibilmente subiranno un'accelerazione «post-COVID»

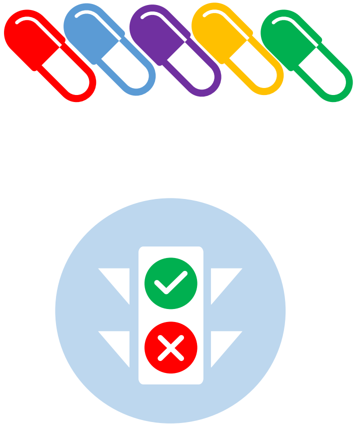
- Più conservativi
- Importante esperienza regolatoria

- Più innovativi
- Meno esperienza regolatoria



Series of independent two-arms RCT

Platform trial without any interim analyses



Platform trial with adaptive elements and GO / NO GO decisions

Platform trial with adaptive elements and GO / NO GO decisions and Bayesian elements

Esempio REMAP-CAP Trial

[Introducing REMAP-CAP (pt.3) on Vimeo]

- Randomised

  Rather than random clinician choice

- Embedded

  Recruitment by clinical staff

  Deliver intervention using usual clinical processes

- Multifactorial

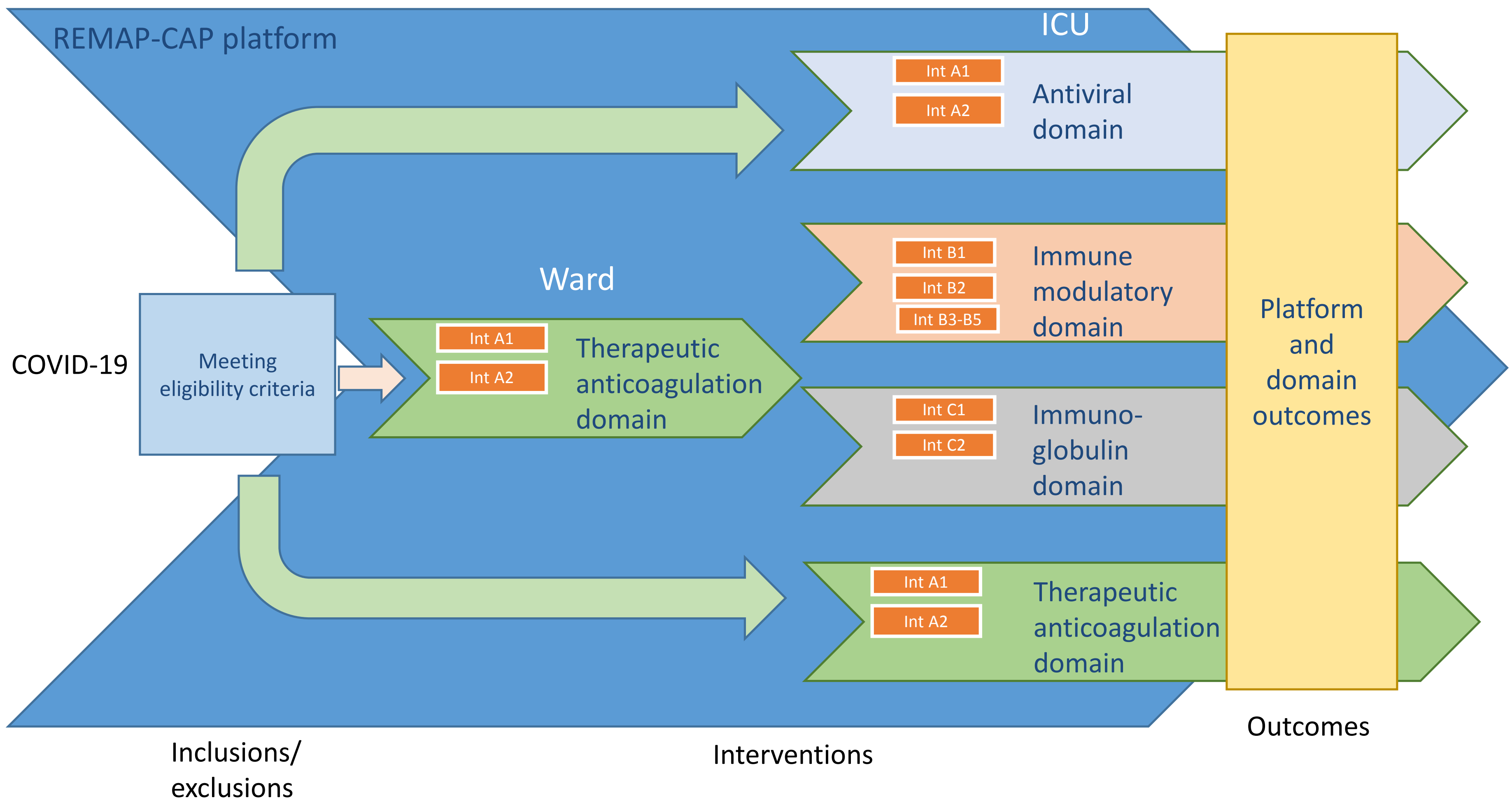
  Simultaneously assess different aspects of treatment

  - Therapeutic anticoagulation (ward and ICU)
  - Antivirals
  - Immunomodulation
  - Immunoglobulin therapy

- Adaptive (frequent Bayesian adaptive analyses & Response adaptive randomization)
- Platform Trial (all patients with COVID-19 included)

PREPARE – Platform foR European Preparedness Against (Re-)emerging Epidemics
UMC Utrecht
CCCTG Canadian Critical Care Trials Group
MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND
anzic research centre

Esempio REMAP-CAP Trial



Esempio REMAP-CAP Trial

- <u>An innovative approach to critical care research</u>: REMAP-CAP uses a novel and innovative adaptive trial design to evaluate a number of treatment options simultaneously and efficiently. This design is able to adapt in the event of pandemics, and increases the likelihood that patients will receive the treatment that is most likely to be effective for them
- <u>Pandemic preparedness</u>: REMAP-CAP provides a global research platform that is able to adapt to efficiently evaluate multiple treatment options for patients who are critically ill due to a global respiratory pandemic

17,407 Patient randomisations	15,614 Patient randomisations with suspected or proven COVID-19	50 Current or completed interventions in 14 Domains
9,753 Total patients	8,661 Patients with suspected or proven COVID-19	340 Active Sites

Platform foR European Preparedness Against (Re-)emerging Epidemics PREPARE

UMC Utrecht

CCCTG Canadian Critical Care Trials Group

MEDICAL RESEARCH INSTITUTE OF NEW ZEALAND

anzic research centre

The White Paper Clinical Research

Joint initiative of key stakeholders involved in clinical research governed by the Swiss Academy of Medical Sciences, published on 22.07.2021

- SCTO, SPHN, SBP, SAKK, SNSF, SERI, patient representatives and representatives from universities, university hospitals, ETH

- To coordinate activities among the involved stakeholders to ensure a clear distribution of tasks and responsibilities and to avoid redundancies

- **To formulate concrete measures to make Switzerland a leading country with highest quality and impactful clinical research**

The White Paper Clinical Research

Based on these considerations, the white paper outlines the following seven goals which constitute an action plan for change to make Switzerland an international leader in patient-centered clinical research:

1. Create a national platform to coordinate publicly funded stakeholders in clinical research
2. Establish strong partnerships with society, citizens, and patients
3. Promote a healthcare system that systematically integrates clinical research: good care comes with – and from – good science
4. Invest in the development of innovative and dynamic clinical research approaches, designs, and technologies enabled by digital tools
5. Strengthen translational, multidisciplinary, and integrated clinical research teams
6. Ensure an environment that is attractive to clinical and health researchers and support them at all career levels
7. Increase the efficiency and accelerate the delivery of clinical research by reducing the complexity of regulatory and data-related processes

Grazie per l’attenzione

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RICERCA

FORMAZIONE

GIORNATA DELLA RICERCA

La Clinical Trial Unit dell’Ente Ospedaliero (CTU-EOC) è membro associato della Swiss Clinical Trial Organization (SCTO), offre servizi di alta qualità per l’implementazione e la conduzione di studi clinici in accordo agli standard nazionali ed internazionali. Aiutando la ricerca clinica e le collaborazioni nazionali ed internazionali, la CTU-EOC permette di offrire ai pazienti cure innovative e di alta qualità.

https://www.ctueoc.ch/