



**NEW TRIAL DESIGNS FOR EARLY DRUG DEVELOPMENT –  
CHALLENGES AND FUTURE VISIONS**

**Dr. Angela Bischoff**

CLINICAL TRIALS SYMPOSIUM

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# CLINICAL RESEARCH STATUS QUO

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- STATE OF THE ART RESEARCH: ONE INDICATION, ONE MOLECULE
- "CLASSIC" PRINCIPLE INVESTIGATOR AND SITE TEAM
- "CLASSIC" PROJECT MANAGEMENT APPROACH
- "CLASSIC" REGULATORY APPROACH

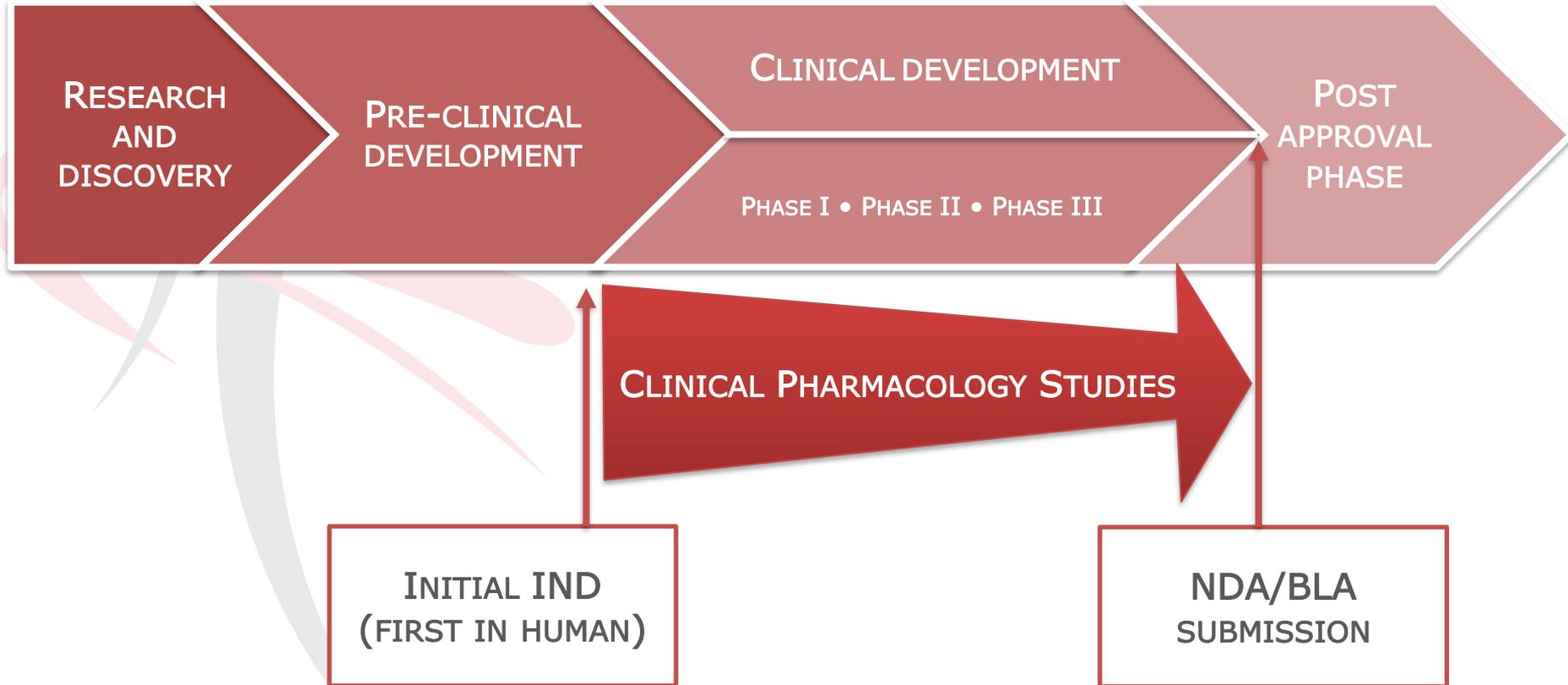
# „CLASSICAL“ CLINICAL RESEARCH

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- **PHASE I:** DETERMINES WHETHER DRUG IS SAFE TO CHECK FOR EFFICACY
  - FURTHER PHASE I: RP2D, FOOD/GENDER/AGE/DDI/BE/PK IN SPECIAL POPULATIONS (RENAL/HEPATIC IMPAIRED)
- **PHASE II:** DETERMINES WHETHER DRUG CAN HAVE ANY EFFICACY, DOSE FINDING FOR CONFIRMATORY TRIALS
- **PHASE III:** DETERMINES A DRUG'S THERAPEUTIC EFFECT
- **POST MARKETING SURVEILLANCE OR PHASE IV:** WATCH DRUG'S LONG TERM EFFECTS

# „CLASSICAL“ CLINICAL RESEARCH

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# TRENDS IN EARLY DEVELOPMENT

	<b>Traditional Design</b>	Drug 1	Indication 1	<ul style="list-style-type: none"> <li>• Single treatment</li> <li>• Single indication</li> </ul>
	<b>Umbrella Design</b>	Drug 1 Drug 2 .... Drug n	Indication 1	<ul style="list-style-type: none"> <li>• Multiple treatments               <ul style="list-style-type: none"> <li>• Fixed # treatment arms or add/delete treatment arms</li> </ul> </li> <li>• Single indication</li> </ul>
	<b>Basket Design</b>	Drug 1	Indication 1 Indication 2 ..... Indication n	<ul style="list-style-type: none"> <li>• Single treatment</li> <li>• Multiple indications               <ul style="list-style-type: none"> <li>• Genomic information</li> <li>• Severity</li> <li>• Lines of therapy</li> <li>• Background Characteristics</li> </ul> </li> </ul>
	<b>Platform Design</b>	Drug 1 Drug 2 .... Drug n	Indication 1 Indication 2 ..... Indication n	<ul style="list-style-type: none"> <li>• Multiple treatments               <ul style="list-style-type: none"> <li>• Fixed # treatment arms or add/delete treatment arms</li> </ul> </li> <li>• Multiple indications               <ul style="list-style-type: none"> <li>• Fixed # indications or add/delete indications</li> </ul> </li> </ul>

# BASKET TRIAL DESIGN

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# BASKET TRIAL DESIGN: **WHY?**

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- MANY MOLECULAR SUBTYPES OF PATHOLOGY DISCOVERED  
→ NARROW "NICHE" INDICATIONS WITH UNIQUE TARGETS
- ENROLLMENT IS A CHALLENGE IN ORPHAN/NICHE INDICATIONS → LACK OF POSSIBILITY TO ENROLL ENOUGH SUBJECTS WITH SPECIFIC DISEASE SUBTYPE
- "ONE INDICATION AT A TIME" NOT FEASIBLE AND NOT EFFECTIVE
- ORIGINAL BASKET TRIAL DESIGN: IMATINIB B2225

# BASKET TRIAL DESIGN: **HOW?**

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- TARGETED THERAPY PAIRED WITH A TARGETABLE MUTATION, IRRESPECTIVE OF CANCER DIAGNOSIS
- CONDITIONS WITH SAME PREDICTIVE BIOMARKERS ARE SELECTED
- MULTIPLE TUMOR TYPES WITH ONE DRUG AND PREDICTIVE BIOMARKER
- USES POOLED POPULATION FOR INITIAL ANALYSIS

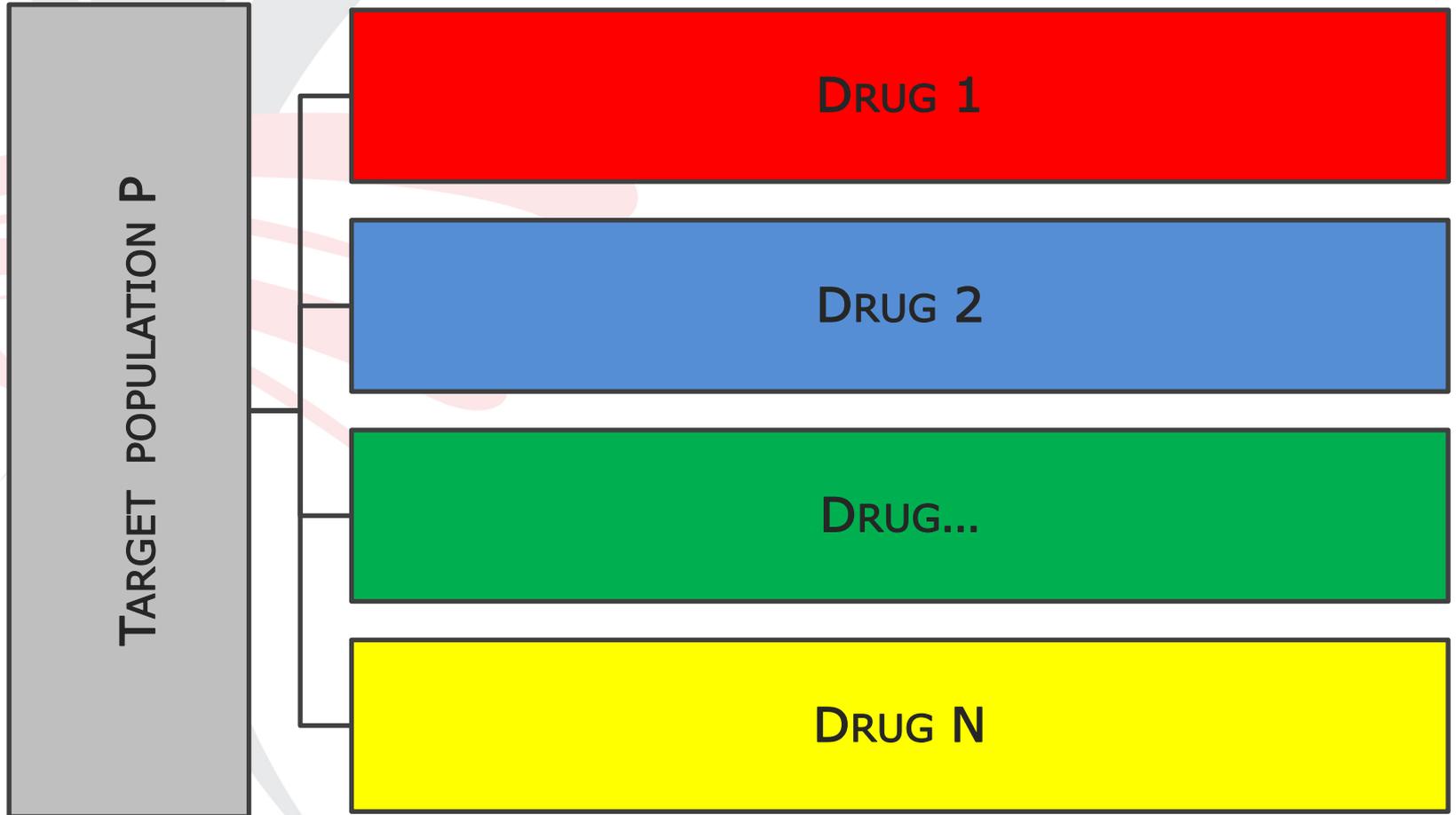
# BASKET TRIAL DESIGN: **BENEFITS**

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- INCREASED AND EARLIER PATIENT ACCESS TO TARGETED THERAPIES FOR SMALL SUBGROUPS
- HYPOTHESIS-DRIVEN MECHANISM OF COMBINING PRECISION MEDICINE WITH CLINICAL TRIAL DESIGN
- VALIDATION OF CLINICAL TARGET
- COST-EFFECTIVE METHODS FOR SPONSORS TO DEVELOP TARGETED AGENTS IN SMALL SUBGROUPS
- DATASETS FOR HEALTH AUTHORITIES TO ASSESS BENEFIT-RISK IN THESE SMALL PATIENT GROUPS

# UMBRELLA TRIAL DESIGN

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# UMBRELLA TRIAL DESIGN: **WHY?**

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- TESTS THE IMPACT OF DIFFERENT DRUGS ON DIFFERENT MUTATIONS IN A SINGLE TYPE OF CANCER OR DIFFERENT MEDICINES IN PATIENTS WITH ONE/SIMILAR DISEASE - '*UNDER THE UMBRELLA OF ONE DISEASE*'
- QUICKER IDENTIFICATION OF PATIENT SUBGROUPS WHO WOULD MOST BENEFIT FROM TESTED MEDICINES
- PERSONALIZED APPROACH FOR TRIAL SUBJECTS → BIGGER SUCCESS RATES

# UMBRELLA TRIAL DESIGN: **HOW?**

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- ONE TUMOR TYPE OR ONE HISTOLOGY TYPE WITH MULTIPLE DRUGS AND PREDICTIVE BIOMARKERS
- PATIENTS ARE MATCHED TO DRUGS BASED ON PREDICTIVE BIOMARKERS → EXPOSURE IS VERY SELECTIVE AND HIGHLY JUSTIFIED (UNNECESSARY EXPOSURE IS AVOIDED)
- COOPERATION AMONG MULTIPLE SPONSORS: COMPOUNDS COULD COME FROM DIFFERENT COMPANIES!

# MASTER PROTOCOLS

	DRUG A	DRUG B	DRUG C	...	DRUG K	...
TYPE 1	<b>BASKET</b>					
TYPE 2						
...						
TYPE N						
...						

	DRUG A	DRUG B	DRUG C	...	DRUG K	...
TYPE 1	<b>UMBRELLA</b>					
TYPE 2						
...						
TYPE N						
...						

	DRUG A	DRUG B	DRUG C	...	DRUG K	...
TYPE 1	<b>PLATFORM</b>					
TYPE 2						
...						
TYPE N						
...						

# PLATFORM TRIAL DESIGN: DEFINITION

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- A PLATFORM TRIAL IS A CLINICAL TRIAL WITH A SINGLE MASTER PROTOCOL IN WHICH MULTIPLE TREATMENTS ARE EVALUATED IN PARALLEL
- ADAPTIVE PLATFORM DESIGNS OFFER FLEXIBLE FEATURES:
  - DROPPING OR ADDING/REPLACEMENT OF TREATMENTS
  - DECLARING ONE OR MORE TREATMENTS AS SUPERIOR

# PLATFORM TRIAL DESIGN: **WHY**

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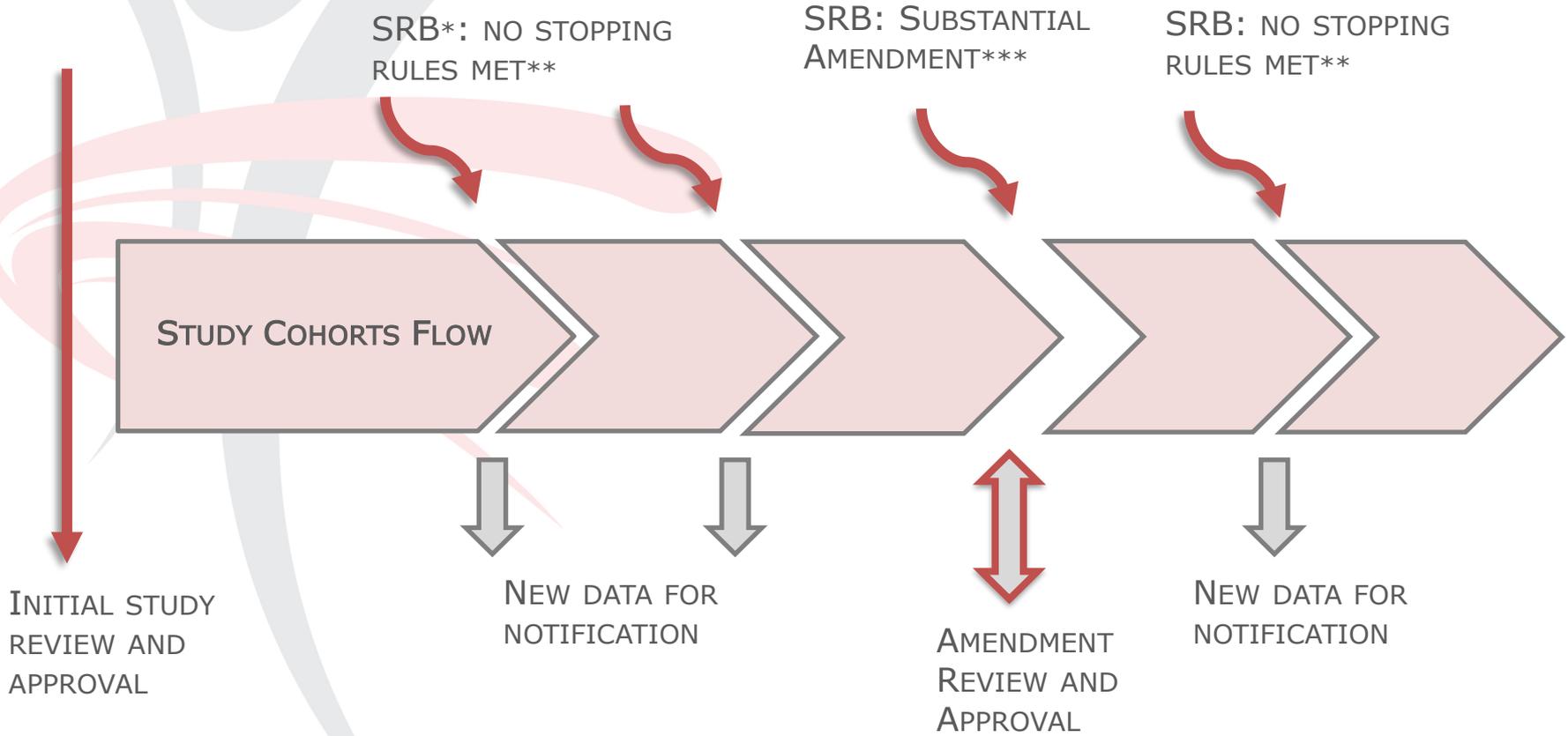
- FIND BENEFICIAL TREATMENTS WITH FEWER PATIENTS, FEWER PATIENT FAILURES, LESS TIME, AND WITH GREATER PROBABILITY OF SUCCESS THAN A TRADITIONAL TWO-ARM STRATEGY
- OBJECTIVE IS GO / NO-GO DECISION OF NEW TREATMENT
- ESCALATION TO PHASE 2A TO PHASE 2B IN EARLY DRUG DEVELOPMENT
- CONSOLIDATED INFORMATION ON DISEASE AS WELL AS TREATMENT

# FDA AND EMA VIEW ON MASTER PROTOCOLS

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- ✓ FDA MODERNIZES CLINICAL TRIAL DESIGNS AND APPROACHES FOR DRUG DEVELOPMENT, PROPOSING NEW GUIDANCE ON THE USE OF ADAPTIVE DESIGNS AND MASTER PROTOCOLS
- ✓ FDA GUIDANCE FOR INDUSTRY (2018): *MASTER PROTOCOLS: EFFICIENT CLINICAL TRIAL DESIGN STRATEGIES TO EXPEDITE DEVELOPMENT OF ONCOLOGY DRUGS AND BIOLOGICS*
- ✓ NEW EMA GUIDELINE (EMA/CHMP/SWP/28367/07 REV. 1) PROVIDES DETAILED RECOMMENDATIONS ON INTEGRATED PROTOCOLS, ESTABLISHING INTEGRATED PROTOCOLS AS AN EU-WIDE ACCEPTED PROTOCOL DESIGN

# REGULATORY OVERSIGHT



*\*SRB – SAFETY REVIEW BOARD*

*\*\* NEXT COHORT AS PREDEFINED BY PROTOCOL ESCALATION STEPS*

*\*\*\* TO INCLUDE NEW DOSE LEVEL, PATIENT POPULATION, COMPOUND/COMBINATION, ETC.*

# WHO MASTER PROTOCOL FOR SARS-COV-2

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- THE WORLD HEALTH ORGANIZATION (WHO) LAUNCHED A MASTER PROTOCOL FOR COMPANIES AND INSTITUTIONS THAT AIM TO TEST THERAPEUTICS AGAINST COVID-19

- THIS TRIAL IS KNOWN UNDER THE NAME **SOLIDARITY**

*“A RANDOMIZED MULTI-CENTER ADAPTIVE CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF INVESTIGATIONAL THERAPEUTIC AGENTS IN COMBINATION WITH STANDARD-OF-CARE FOR THE TREATMENT OF HOSPITALIZED PATIENTS WITH NOVEL CORONAVIRUS DISEASE (COVID-19).”*

- THE DESIGN IS AN ADAPTIVE UMBRELLA MASTER PROTOCOL (SIMILARLY USED FOR EBOLA)
- THE SOLIDARITY TRIAL COMPARES OPTIONS AGAINST STANDARD OF CARE, TO ASSESS THEIR RELATIVE EFFECTIVENESS AGAINST COVID-19

- Source: [https://www.who.int/blueprint/priority-diseases/key-action/COVID-19\\_Treatment\\_Trial\\_Design\\_Master\\_Protocol\\_synopsis\\_Final\\_18022020.pdf](https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)

# WHO MASTER PROTOCOL FOR SARS-COV-2

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- THE SOLIDARITY TRIAL HAS A PILOT STAGE AND A PIVOTAL STAGE. THE PILOT STAGE WILL HAVE ABOUT 50 TO 100 PARTICIPANTS RANDOMIZED TO ONE OF THE VARIOUS INVESTIGATIONAL AGENTS OR STANDARD-OF-CARE AS THE CONTROL. THE WHO WILL USE THE RESULTS FROM THE PILOT PHASE TO INFORM THE DESIGN OF THE PIVOTAL PHASE AND IDENTIFY MARKERS OF DISEASE EVOLUTION AND CLINICAL BENEFITS.
- ONCE THE PIVOTAL PHASE IS STARTED, THE INVESTIGATIONAL AGENTS WOULD BE TESTED “UNTIL THERE IS AVAILABLE EVIDENCE THAT THEY HAVE A FAVORABLE BENEFIT-RISK PROFILE OR UNTIL FUTILITY IS ESTABLISHED; ACCORDING TO A PRIOR ESTABLISHED CLINICAL AND STATISTICAL CRITERIA.”

# WHO MASTER PROTOCOL FOR SARS-COV-2

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## RATIONALE

THE PRESSURE COVID-19 PUTS ON HEALTH SYSTEMS MEANS THAT WHO CONSIDERED THE NEED FOR SPEED AND SCALE IN THE TRIAL. WHILE RANDOMIZED CLINICAL TRIALS NORMALLY TAKE YEARS TO DESIGN AND CONDUCT, THE SOLIDARITY TRIAL WILL REDUCE THE TIME TAKEN BY 80%.

## PARTICIPATION IN SOLIDARITY

AS OF 1 JULY 2020, NEARLY 5500 PATIENTS HAVE BEEN RECRUITED IN 21 COUNTRIES AMONG THE 39 COUNTRIES THAT HAVE APPROVALS TO BEGIN RECRUITING. OVERALL, OVER 100 COUNTRIES IN ALL 6 WHO REGIONS HAVE JOINED OR EXPRESSED AN INTEREST IN JOINING THE TRIAL, AND WHO IS ACTIVELY SUPPORTING THEM WITH:

- ETHICAL AND REGULATORY APPROVALS OF THE WHO CORE PROTOCOL;
- IDENTIFICATION OF HOSPITALS PARTICIPATING IN THE TRIAL;
- TRAINING OF HOSPITAL CLINICIANS ON THE WEB-BASED RANDOMIZATION AND DATA SYSTEM;
- SHIPPING THE TRIAL DRUGS AS REQUESTED BY EACH PARTICIPATING COUNTRY.

# COVID-19 MASTER PROTOCOLS GENERIC DRUGS

## COVID-19 Master Protocol Trials

	RECOVERY	ACTT	SOLIDARITY	REMAP-CAP
<b>Sponsor</b>	University of Oxford	National Institute of Allergy and Infectious Disease (NIAID)	World Health Organization (WHO)	MJM Bonten, UMC Utrecht
<b>Arms</b>	Lopinavir/ritonavir; Dexamethasone; Hydroxychloroquine; Interferon- $\beta$	Remdesivir; placebo	Hydroxychloroquine or chloroquine; Remdesivir; Lopinavir/ritonavir; Interferon- $\beta$ and lopinavir/ritonavir; Standard of care	Hydroxychloroquine; Hydroxychloroquine plus lopinavir/ritonavir; Interferon- $\beta$ ; Anakinra (IL-1RA antagonist); Standard of care
<b>Trial design</b>	Randomized adaptive trial	Randomized, placebo-controlled adaptive trial	Randomized adaptive trial	Randomized adaptive trial
<b>Primary endpoint</b>	In-hospital mortality, 28 days	Disease severity, measured by 8-point scale	Disease severity	Days alive and outside ICU
<b>Target enrollment</b>	5000	400 (Initial)	Undetermined	6800
<b>Location</b>	U.K.	International	International	International

**BIOCENTURY**

# COVID-19 PROTOCOLS REGISTERED

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IN PUBLIC REGISTERS FOUND BY 07 OCTOBER 2020

- COVID-19 TRIALS IN TOTAL: N= 3711
- COVID TRIALS ANTIVIRAL: N= 285
- **COVID-19 TRIALS ADAPTIVE DESIGNS: N= 96**
- COVID-19 TRIALS WITH MONOCLONAL ABS N= 46
- COVID-19 VACCINE TRIALS: N= 228

# COVID-19 MASTER PROTOCOLS ARENZIA'S EXPERIENCE

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- SAFETY, TOLERABILITY, AND EFFICACY OF ANTI-SPIKE (S) SARS-CoV-2 MONOCLONAL ANTIBODIES FOR THE TREATMENT OF AMBULATORY ADULT PATIENTS WITH COVID-19  
<https://clinicaltrials.gov/ct2/show/NCT04425629?term=REGN10933&draw=2&rank=3>
- SAFETY, TOLERABILITY, AND EFFICACY OF ANTI-SPIKE (S) SARS-CoV-2 MONOCLONAL ANTIBODIES FOR HOSPITALIZED ADULT PATIENTS WITH COVID-19  
<https://clinicaltrials.gov/ct2/show/NCT04426695?term=REGN10933&draw=2&rank=4>

# CONCLUSION AND FUTURE VIEWS

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- ADAPTIVE MASTER PROTOCOLS ARE OFFERING THE FASTEST PATH TO INVESTIGATE THE SAFEST AND MOST EFFECTIVE TREATMENTS FOR COVID-19.
- THE SUCCESS OF MASTER PROTOCOLS FIGHTING COVID-19 WILL MAKE THIS DESIGN MORE VALUABLE AND VISIBLE ALSO FOR USE IN STANDARD DRUG DEVELOPMENT IN FUTURE
- THESE LARGE-SCALE TRIALS SIMULTANEOUSLY EVALUATE MULTIPLE TREATMENTS OR PATIENT POPULATIONS UNDER A SINGLE STUDY PROTOCOL AND SET OF ENDPOINTS.
- THE BENEFITS ARE EFFICIENCY, WHICH COMES FROM THE PARALLEL TESTING AND SHARING OF A CONTROL ARM, AND GENERATION OF DATA THAT CAN BE MEANINGFULLY COMPARED ACROSS TREATMENTS
- FOR COVID-19 THERAPIES, THE FOCUS IS ON ADAPTIVE TRIALS, WHICH EVALUATE MULTIPLE TREATMENTS IN A SINGLE POPULATION WITH A SINGLE STANDARD OF CARE CONTROL ARM. AT INTERIM ANALYSIS POINTS, TREATMENT ARMS CAN BE ADDED OR DROPPED, AND THE TRIAL CAN BE DESIGNED TO CONTINUE WITH DIFFERENT TREATMENT ARMS INDEFINITELY.



# THANK YOU!

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FOR ANY QUESTIONS PLEASE CONTACT:

ANGELA BISCHOFF

CELL: +49 152 51920 475

[ANGELA.BISCHOFF@ARENSIA-EM.COM](mailto:ANGELA.BISCHOFF@ARENSIA-EM.COM)

[WWW.ARENSIA-EM.COM](http://WWW.ARENSIA-EM.COM)

# REFERENCES AND EXAMPLES: PLATFORM TRIAL DESIGN

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- **I-SPY 2** (<https://clinicaltrials.gov/ct2/show/NCT01042379?term=i-spy2&rank=1>)
  - **INDICATION:** EARLY HIGH RISK BREAST CANCER, 1920 PATIENTS
  - **DESIGN:** PHASE 2, MULTICENTER, ADAPTIVE, RANDOMISED
  - **IMPs:** 19 DIFFERENT TREATMENT, EITHER SINGLE OR COMBINED
    - PEMBROLIZUMAB, TRASTUZUMAB, PERTUZUMAB, NERATINIB
    - AND MORE...
  - **TUMOR CHARACTERISTICS:** MAMMAPRINT HIGH, ANY ER STATUS, ANY HER2 STATUS, OR MAMMAPRINT LOW, ER NEGATIVE (<5%), ANY HER2 STATUS, OR MAMMAPRINT LOW, ER POSITIVE, HER2/NEU POSITIVE

# REFERENCES AND EXAMPLES: UMBRELLA TRIAL DESIGN

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- BATTLE (BIOMARKER-INTEGRATED APPROACHES OF TARGETED THERAPY FOR LUNG CANCER ELIMINATION) TRIAL
- WINTHER (A STUDY TO SELECT RATIONAL THERAPEUTICS BASED ON THE ANALYSIS OF MATCHED TUMOR AND NORMAL BIOPSIES IN SUBJECTS WITH ADVANCED MALIGNANCIES)
- MATCH (MOLECULAR ANALYSIS FOR THERAPY CHOICE) TRIAL

# REFERENCES AND EXAMPLES: BASKET TRIAL DESIGN

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- 2015: NATIONAL CANCER INSTITUTE US: NCI-MATCH TRIAL (MOLECULAR ANALYSIS FOR THERAPY CHOICE), WITH PLANS TO SCREEN UP TO 3,000 PATIENTS WITH ENROLLMENT OF AT LEAST 1,000 INDIVIDUALS TO A TARGETED DRUG COMBINATION, INDEPENDENT OF TUMOR HISTOLOGY
- NCI-IMPACT TRIAL (MOLECULAR PROFILING-BASED ASSIGNMENT OF CANCER T
- CUSTOM (MOLECULAR PROFILING AND TARGETED THERAPIES IN ADVANCED THORACIC MALIGNANCIES) TRIAL THERAPY

# REFERENCES AND EXAMPLES: FDA AND EMA VIEW ON MATER PROTOCOLS

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<https://www.fda.gov/news-events/fda-brief/fda-brief-fda-modernizes-clinical-trial-designs-and-approaches-drug-development-proposing-new>

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and-biologics>

[https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf)

# REFERENCES AND EXAMPLES: FDA APPROVALS BASED ON MASTER PROTOCOLS

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- 2017: **PEMBROLIZUMAB (KEYTRUDA)**  
FOR AN EXPANDED INDICATION TO TREAT  
MICROSATELLITE INSTABILITY-HIGH CANCER BASED  
ONLY ON GENETIC ABNORMALITY, REGARDLESS OF  
ORIGIN OR LOCATION
- 2018: **LAROTRECTINIB (VITRAKVI)**
- FOR ADULT AND PEDIATRIC PATIENTS WITH SOLID  
TUMORS THAT HAVE A NEUROTROPHIC RECEPTOR  
TYROSINE KINASE (NTRK) GENE FUSION WITHOUT A  
KNOWN ACQUIRED RESISTANCE MUTATION

# REFERENCES AND EXAMPLES: COVID TRIALS

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- [https://www.who.int/blueprint/priority-diseases/key-action/COVID19 Treatment Trial Design Master Protocol synopsis Final 18022020.pdf](https://www.who.int/blueprint/priority-diseases/key-action/COVID19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf)
- <https://clinicaltrials.gov/ct2/results?cond=&term=COVID-19+vaccine&cntry=&state=&city=&dist=>